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THE UNIVERSITY OF ALBERTA

SOME STUDIES ON THE CHEMISTRY OF 1,2-DIHYDROPYRIDINES

by

© THEODORE ADAM ONDRUS

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE

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EDMONTON, ALBERTA

FALL, 1977

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled .....

SOME STUDIES ON THE CHEMISTRY OF 1,2-DIHYDROPYRIDINES

.....

submitted by THEODORE ADAM ONDRUS

in partial fulfilment of the requirements for the degree of Master of Science in Pharmaceutical Chemistry.

E. E. Knaus

(Supervisor)

R. J. Coutts

(External Examiner)

Date July 14, 1977

TO MAUREEN

ARSTRACT

Reaction of the ambident anion N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) with several electrophilic reagents has been investigated. Reaction of XXX with ethyl acetate and diethylchlorophosphate yielded N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) and N-diethylphosphoryl-2-n-butyl-1,2-dihydropyridine (LIX). Reaction of XXX with cyclohexylisocyanate gave rise to a mixture of N-(N-cyclohexyl)carboxamido-2-n-butyl-1,2-dihydropyridine (LX) and 5-(N-cyclohexyl)carboxamido-2-n-butylpyridine (LXI). Reaction of XXX with chloramine, cyanogen bromide, N-bromosuccinimide, phenylselenyl chloride, N-methanesulfonylpyridinium chloride, methyl p-toluenesulfonate and methyl trifluoromethanesulfonate affords 2,5-disubstituted pyridines.

Reaction of N-diethylphosphoryl-2-n-butyl-1,2-dihydropyridine (LIX) with 1,2,4-triazoline-3,5-dione afforded the endo $\pi 2 + \pi 4$ cycloaddition product (LXIX). Stereochemistry was assigned on the basis of nmr data.

Reaction of several 1,2-dihydropyridines with cyanogen azide has been investigated. Reaction of 1,2-dihydropyridines with cyanogen azide affords 2,7-diazabicyclo [4.1.0] hept-4-enes. Treatment of 2,7-diazabicyclo [4.1.0] hept-4-enes with neutral alumina oxide gave rise to tetrahydropyridylidene-2-cyanamides. Reduction of 2,7-diazabicyclo [4.1.0] hept-4-enes and tetrahydropyridylidene-2-cyanamides using 10% palladium - charcoal and hydrogen gas affords a tautomeric mixture of piperidylidene-2-cyanamides and tetrahydropyridyl-2-cyanamides. Acid hydrolysis of the tautomeric mixture affords 2-piperidones. In

contrast, reaction of N-methoxycarbonyl- and N-methanesulfonyl-1,2-dihydropyridines with cyanogen azide gave rise to a 1:1 isomeric mixture of syn-N-substituted-1,2,3,4-tetrahydropyridylidene-4-cyanamides and anti-N-substituted-1,2,3,4-tetrahydropyridylidene-4-cyanamides. The presence of a 1:1 isomeric mixture was confirmed using nmr double irradiation experiments and temperature studies. Reaction of N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) with cyanogen azide gave rise to the isomeric mixture of syn-tetrahydropyridylidene-4-cyanamide (XCIa) and anti-tetrahydropyridylidene-4-cyanamide (XCIb) as well as the unexpected 2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII) and 2-diazo-1,2,3,6-tetrahydropyridylidene-3-cyanamide (XCII).

Reaction of 2-n-butyl-1,2-dihydropyridine (LVI) with several sulfonyl azides, carbonyl azides and hydrazoic acid has been investigated. Reaction of LVI with sulfonyl azides in the presence of lithium hydroxide (5%) affords 3-diazo-1,2,3,6-tetrahydropyridylidene-2-sulfonamides and 2,7-diazabicyclo [4.1.0] hept-4-enes. Reaction of LVI with sulfonyl azides in the absence of lithium hydroxide gave rise to 2,7-diazabicyclo [4.1.0] hept-4-enes in quantitative yield. Treatment of 2,7-diazabicyclo [4.1.0] hept-4-enes with neutral alumina oxide gave rise to tetrahydropyridylidene-2-sulfonamides. Reduction of 2,7-diazabicyclo [4.1.0] hept-4-enes and tetrahydropyridylidene-2-sulfonamides with 10% palladium - charcoal and hydrogen gas affords piperidylidene-2-sulfonamides. Reaction of LVI with benzoyl azide affords tetrahydropyridylidene-2-phenylcarbonylamide (CXI). Reaction of LVI with methoxycarbonyl azide gave rise to 2,7-diazabicyclo

[4.1.0] hept-4-ene (CXII) in quantitative yield. Chromatography of CXII on silica gel G plates affords tetrahydropyridylidene-2-methoxycarbonylamide (CXIII). Reduction of CXII using 10% palladium - charcoal and hydrogen gas affords the tautomeric mixture of the piperidylidene-2-methoxycarbonylamide (CXIVa) and tetrahydropyridyl-2-methoxycarbonylamide (CXIVb). Reaction of LVI with hydrazoic acid gave rise to 6,6'-di-n-butyl-1,2,3,6-tetrahydro-2,3'-dipyridyl (LXIII).

Reaction of N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) with benzene sulfonyl azide affords 2,7-diazabicyclo [4.1.0] hept-4-ene (CIV).

ACKNOWLEDGMENTS

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TABLE OF CONTENTS

CHAPTER		PAGE
1.0.0.0.0	INTRODUCTION	1
1.1.1.0.0	Pharmacological properties of some 3-substituted pyridine derivatives	2
1.1.2.0.0	Pharmacological properties of some 1,2-dihydropyridine derivatives	5
1.1.3.0.0	Pharmacological properties of some fused aziridine derivatives of tetrahydropyridines	6
1.2.1.0.0	Physical properties of 1,2-dihydropyridines.....	7
1.2.2.0.0	Synthesis of some simple 1,2-dihydropyridines	8
1.2.2.1.0	Reductions of pyridinium salts with sodium borohydride	8
1.2.2.2.0	Reduction of pyridine by lithium aluminum hydride	9
1.2.2.3.0	Nucleophilic additions of organometallic reagents to pyridinium salts.....	10
1.2.2.4.0	Nucleophilic additions of organometallic reagents to pyridines	11
1.2.3.0.0	Some chemistry of 1,2-dihydropyridines	13
1.2.3.1.0	Reactions of 1,2-dihydropyridines with complex hydrides	13
1.2.3.2.0	Reactions of organometallic - pyridine adducts with carbonyls	14
1.2.3.3.0	Reactions of organometallic - pyridine adducts with electrophiles	14
1.2.3.4.0	Some cycloaddition reactions of 1,2-dihydropyridines	22

CHAPTER		PAGE
1.2.4.0.0	Some 1,3-dipolar cycloaddition reactions	23
1.2.4.1.0	Reactions of organic azides with enamines	26
2.0.0.0.0	OBJECTS OF RESEARCH	28
3.0.0.0.0	DISCUSSION	29
3.1.0.0.0	Reactions of N-lithio-2-n-butyl-1,2-dihydropyridine and 2-n-butyl-1,2-dihydropyridine with electrophiles	29
3.1.1.0.0	Synthesis of N-substituted-1,2-dihydropyridines	29
3.1.2.0.0	Synthesis of 2,5-disubstituted pyridines	32
3.2.0.0.0	Diels-Alder cycloaddition of 4-phenyl-1,2,4-triazoline-3,5-dione with a N-substituted-1,2-dihydropyridine	36
3.3.0.0.0	Reactions of organic azides with pyridines and 1,2-dihydropyridines	37
3.3.1.0.0	Reactions of cyanogen azide with pyridines	38
3.3.2.0.0	Reactions of organic azides with 1,2-dihydropyridines	39
3.3.2.1.0	Reactions of cyanogen azide with 1,2-dihydropyridines	40
3.3.2.2.0	Reactions of cyanogen azide with N-substituted-1,2-dihydropyridines	51
3.3.2.3.0	Reactions of 1,2-dihydropyridines with sulfonyl azides, carbonyl azides and hydrazoic acid	66
3.3.2.4.0	Reactions of N-substituted-1,2-dihydropyridines with benzenesulfonyl azide	73
3.4.0.0.0	Broad spectrum pharmacological screening	75

CHAPTER		PAGE
4.0.0.0.0	EXPERIMENTAL	78
4.1.0.0.0	Solvents and reagents	78
4.2.0.0.0	Reactions of N-lithio-2-n-butyl-1,2-dihydropyridine and 2-n-butyl-1,2-dihydropyridine with electrophiles	80
4.2.1.0.0	Preparation of N-lithio-2-n-butyl-1,2-dihydropyridine and 2-n-butyl-1,2-dihydropyridine	80
4.2.2.1.1	Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with ethyl acetate	80
4.2.2.2.1	Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with diethylchlorophosphate	81
4.2.2.2.2	Reaction of 2-n-butyl-1,2-dihydropyridine with diethylchlorophosphate	82
4.2.2.2.3	Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with cyclohexylisocyanate	83
4.2.2.3.1	Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with chloramine	84
4.2.2.4.1	Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with cyanogen bromide	85
4.2.2.4.2	Reaction of 2-n-butyl-1,2-dihydropyridine with cyanogen bromide	86
4.2.2.4.3	Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with cyanogen bromide using an inverse addition procedure	86
4.2.2.5.1	Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with N-bromosuccinimide using an inverse addition procedure	87
4.2.2.6.1	Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with N-methanesulfonylpyridinium chloride	88
4.2.2.6.2	Reaction of 2-n-butyl-1,2-dihydropyridine with N-methanesulfonylpyridinium chloride	88

CHAPTER		PAGE
4.2.2.7.1	Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with phenylselenyl chloride	89
4.2.2.7.2	Reaction of 2-n-butyl-1,2-dihydropyridine with phenylselenyl chloride	90
4.2.2.8.1	Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with methyl p-toluenesulfonate	90
4.2.2.8.2	Reaction of 2-n-butyl-1,2-dihydropyridine with methyl p-toluenesulfonate	91
4.2.2.8.3	Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine with methyl trifluoromethanesulfonate	91
4.2.2.8.4	Reaction of 2-n-butyl-1,2-dihydropyridine with methyl trifluoromethanesulfonate	91
4.3.1.0.0	Reaction of N-diethylphosphoryl-2-n-butyl-1,2-dihydropyridine with 4-phenyl-1,2,4-triazoline-3,5-dione	92
4.4.0.0.0	Reactions of 1,2-dihydropyridines with organic azides	93
4.4.1.1.0	Preparation of cyanogen azide	93
4.4.1.2.0	Preparation of lithium hydroxide free 2-n-butyl-1,2-dihydropyridine	93
4.4.2.1.1	Reaction of 2-mercaptopyridine with cyanogen azide	94
4.4.2.1.2	Reaction of 2-mercaptopyridine with cyanogen bromide	95
4.4.2.2.1	Reaction of 2-mercaptopyridine-N-oxide with cyanogen azide	95
4.4.2.3.1	Reaction of 2-n-butyl-1,2-dihydropyridine with cyanogen azide	96
4.4.2.3.2	Ring opening of 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene	96

CHAPTER		PAGE
4.4.2.3.3	Reduction of 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene and 6-n-butyl-1,2,5,6-tetrahydropyridyl-idene-2-cyanamide	97
4.4.2.4.1	Reaction of 2-phenyl-1,2-dihydropyridine with cyanogen azide	98
4.4.2.4.2	Ring opening of 3-phenyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene	99
4.4.2.4.3	Reduction of 3-phenyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene and 6-phenyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide	99
4.4.2.4.4	Hydrolysis of 6-phenylpiperidylidene-2-cyanamide and 6-phenyl-3,4,5,6-tetrahydro-pyridyl-2-cyanamide	100
4.4.2.5.1	Reaction of N-methoxycarbonyl-1,2-dihydro-pyridine with cyanogen azide	101
4.4.2.6.1	Reaction of N-methanesulfonyl-1,2-dihydro-pyridine with cyanogen azide	102
4.4.2.7.1	Reaction of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine with cyanogen azide	103
4.4.2.8.1	Reaction of N-methoxycarbonyl-2-n-butyl-1,2-dihydropyridine with cyanogen azide	104
4.4.2.9.1	Reaction of N-acetyl-2-n-butyl-1,2-dihydro-pyridine with cyanogen azide	105
4.4.3.1.1	Reaction of 2-n-butyl-1,2-dihydropyridine with methanesulfonyl azide	107
4.4.3.1.2	Ring opening of 3-n-butyl-7-methanesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene	109
4.4.3.1.3	Reduction of 3-n-butyl-7-methanesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene and 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-methanesulfonamide	109

CHAPTER		PAGE
4.4.3.2.1	Reaction of 2-n-butyl-1,2-dihydropyridine with benzenesulfonyl azide	110
4.4.3.3.1	Reaction of 2-n-butyl-1,2-dihydropyridine with N-acetylsulfanilyl azide	112
4.4.3.4.1	Reaction of 2-n-butyl-1,2-dihydropyridine with sulfanilyl azide	114
4.4.3.4.2	Ring opening of 3-n-butyl-7-sulfanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene	115
4.4.3.4.3	Reduction of 3-n-butyl-7-sulfanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene and 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-sulfanilamide	116
4.4.3.5.1	Reaction of 2-n-butyl-1,2-dihydropyridine with benzoyl azide	116
4.4.3.6.1	Reaction of 2-n-butyl-1,2-dihydropyridine with methoxycarbonyl azide	118
4.4.3.6.2	Ring opening of 3-n-butyl-7-methoxycarbonyl-2,7-diazabicyclo [4.1.0] hept-4-ene	118
4.4.3.6.3	Reduction of 3-n-butyl-7-methoxycarbonyl-2,7-diazabicyclo [4.1.0] hept-4-ene	119
4.4.3.7.1	Reaction of 2-n-butyl-1,2-dihydropyridine with hydrazoic acid	120
4.4.3.8.1	Reaction of N-acetyl-2-n-butyl-1,2-dihydropyridine with benzenesulfonyl azide	120
	* * *	
5.0.0.0.0	BIBLIOGRAPHY	122

LIST OF FIGURES

Figure | Page

1. NMR temperature study of N-methoxycarbonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide 55

LIST OF SCHEMES

Scheme		Page
1.	Fragmentation of N-acetyl-2-n-butyl-1,2-dihydropyridine	31
2.	Major fragmentations of 3-n-butyl-7-cyano-2,7-diaza-bicyclo [4.1.0] hept-4-ene	42
3.	Major fragmentations of 6-n-butyl-1,2,5,6-tetra-hydropyridylidene-2-cyanamide	46
4.	Major fragmentation of the tautomeric mixture of 6-n-butylpiperidylidene-2-cyanamide and 6-n-butyl-1,2,3,4-tetrahydropyridyl-2-cyanamide	49
5.	Major fragmentations of the 1:1 isomeric mixture of <u>syn</u>-N-methoxycarbonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide and <u>anti</u>-N-methoxycarbonyl-1,2,3,4-tetra-hydropyridylidene-4-cyanamide	58

1.0.0.0.0 INTRODUCTION

The chemistry and pharmacology of dihydropyridines has been actively investigated since the original synthesis was published by Hantzsch[1] in 1882. The majority of studies before the discovery of the reduced form of nicotinamide adenine dinucleotide (NADH) were modifications of the original synthesis. The structure and physiological role of NADH stimulated further work on model dihydropyridines which were synthesized by a variety of methods. Limited instrumental techniques initially hindered the differentiation of isomers, causing much confusion in the early literature as to the actual structures of dihydropyridines synthesized. Later, with advances in spectroscopic techniques, the structures of these compounds were unambiguously assigned.

A review of the earlier studies up to 1957 has appeared[2] but was written from the point of view of pyridine synthesis. More recently, a detailed review on the chemistry of dihydropyridines has been published[3]. An excellent review covering the pharmacologically interesting pyridines and reduced pyridine derivatives is available[4].

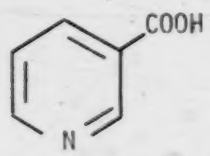
The chemistry of 1,2-dihydropyridine derivatives has also been examined in great depth and a recent review[3] summarizes the majority of these results.

The pharmacology of 1,2-dihydropyridines has received little attention to date. The pharmacological properties exhibited by 1,2-dihydropyridines as well as some pyridine and tetrahydropyridine derivatives prepared from 1,2-dihydropyridine intermediates will be presented in the subsequent sections.

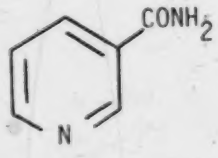
1.1.1.0.0 Pharmacological properties of some 3-substituted pyridine derivatives

The beta (β)- or 3-substituted pyridines which can be prepared from 1,2-dihydropyridines serve as important intermediates in the synthesis of biologically active pyridine derivatives.

Many pharmacologically active pyridines are derivatives of nicotinic acid (niacin) (I). One of the most obvious examples is nicotinamide (niacinamide) (II) which is a member of the vitamin B group. The tuberculostatic activity and vitamin properties of niacinamide are well known.

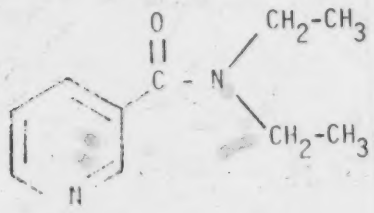


I



II

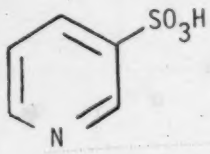
N,N-Diethylnicotinamide (III), a derivative of nicotinamide exhibits moderate CNS stimulant activity[5].



III

Some microorganisms require the preformed coenzymes diphosphopyridine nucleotide (DPN) and triphosphopyridine nucleotide (TPN)

for growth and reproduction. Others are capable of synthesizing the coenzyme from niacin and niacinamide. Compounds such as pyridine-3-sulfonic acid (IV), pyridine-3-sulfonamide[6] (V), 3-acetylpyridine[7] (VI), halogen substituted nicotinic acids[8] (VII) and 6-aminonicotinamide[9] (VIII) can act as antagonists of niacin or niacinamide, inhibiting the growth of these organisms.



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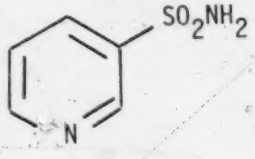

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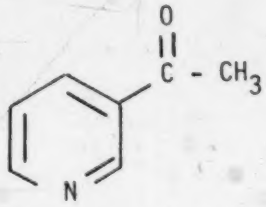
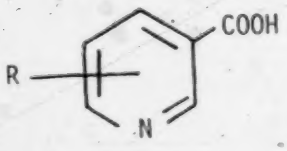
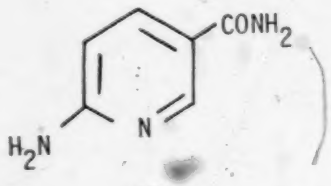


VI

R = (C_2)F
R = (C_6)F
R = (C_5)F,Cl,Br

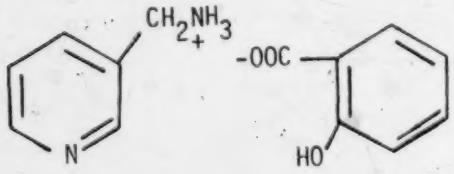


VII

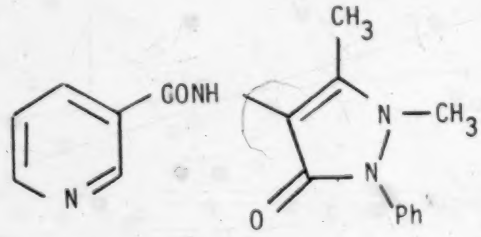


VIII

A potent pyridine analgesic, 3-pyridylmethylammonium salicylate (IX) is described as an antirheumatic and analgesic for external use[10]. Nifenazone (X) exhibits analgesic and antiinflammatory properties.



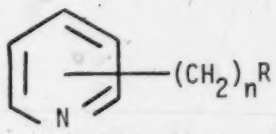
IX



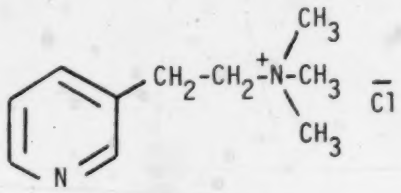
X

The evaluation[11] of a large number of pyridine derivatives for

their ganglionic stimulating properties included those of general structure XI where n was 1 or 2 and the point of attachment was the 2, 3 or 4 position of the pyridine ring. The R substituent was pyrrolidine, piperidine or a trialkylammonium group. The most active compounds possessed a quaternary ammonium group with a chain attached at the 3 position of the pyridine ring. One example is structure XII.

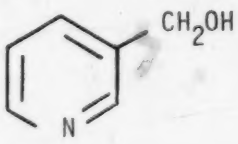


XI

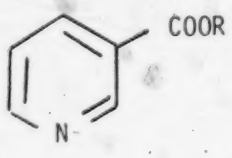


XII

Another 3-substituted pyridine, 3-pyridylcarbinol (XIII) is used commercially as a vasodilator[12]. It has a long duration of action compared to nicotinic acid and is also active orally. Nicotinic esters XIV also exhibit vasodilator properties[13].



XIII



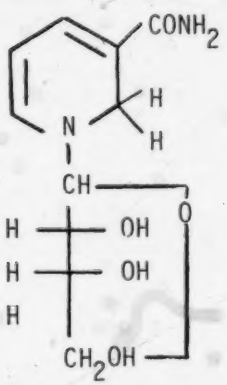
XIV

R = CH_3, $CH(CH_3)_2$, CH_2Ph

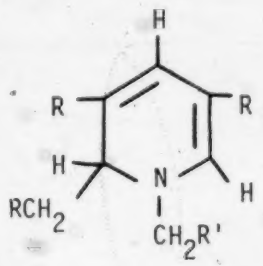
Many other pharmacologically active 3-substituted pyridine derivatives have been prepared. The examples described were selected to emphasize the variety of activities which 3-substituted pyridines exhibit.

1.1.2.0.0 Pharmacological Properties of some 1,2-dihydropyridine derivatives

To date there have been very few studies on the pharmacology of 1,2-dihydropyridines. One study reported the preparation of 1,2-dihydronicotinamide-D-ribofuranoside (XV) as an intermediate product in the synthesis of Coenzyme I[14]. However, a more recent report has shown XV to be the 1,4-dihydronicotinamide isomer[14a]. Another report[15] described the preparation of 1,2-dihydropyridine XVI as an intermediate in the formation of isodesmosine. Isodesmosine, a quaternary pyridinium salt, forms the cross linkage of elastin.



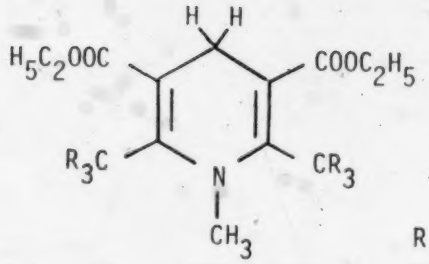
XV



XVI

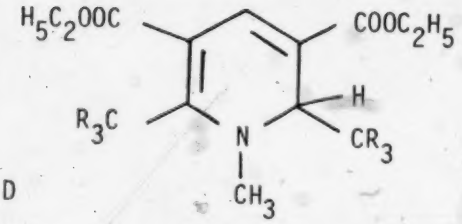
R,R' = CH_3CH_2-, $CH_3CH_2CH_2$-; CH_3CH_2-, $CH_3(CH_2)_3CH_2$-; CH_3CH_2-, CH_3O_2C-; $CH_3(CH_2)_2CH_2$-, $CH_3(CH_2)_3CH_2$-

An investigation[16] into the mechanism of a pyridine nucleotide transhydrogenase has reported the hydride mobility in pyridinium salt - dihydropyridine mixtures. This study concludes that the 1,4-dihydropyridine XVII is an excellent hydride donor. The corresponding 1,2-dihydropyridine XVIII is described as unreactive under mild conditions and is also reported to serve as a hydride trap at elevated temperatures.



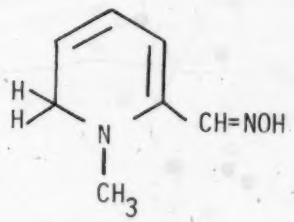
XVII

R = H,D

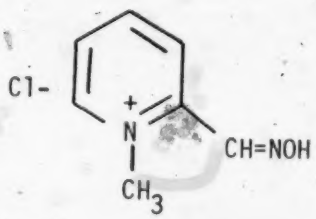


XVIII

Studies have been reported recently which utilize the 1,6-dihydropyridine derivative XIX as a pro-drug to N-methylpyridinium-2-carbaldoxime chloride, a quaternary pyridinium salt XX which is used as an acetylcholinesterase reactivator. The amount of 1,6-dihydropyridine XIX delivered across the blood brain barrier is thirteen times that of the salt XX[17].



XIX

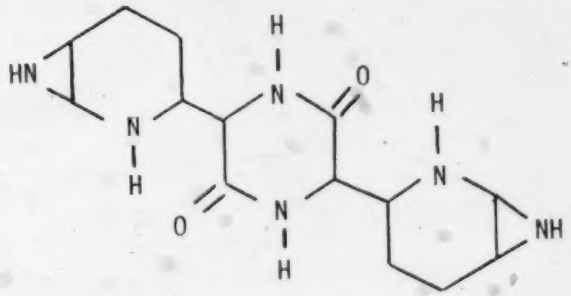


XX

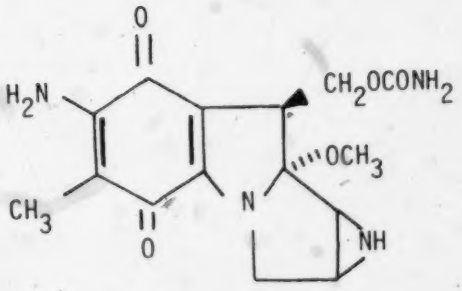
1.1.3.0.0 Pharmacological properties of some fused aziridine derivatives of tetrahydropyridines

The pharmacological properties of 2,7-diazabicyclo [4.1.0] hept-4-enes have not been reported to date although a recent patent[18] describes the preparation and testing of a compound containing the fully saturated system. For example, 3,6-{3-(2,7-diazabicyclo [4.1.0] heptyl)}-2,5-piperazinedione (XXI) has been reported to

inhibit the growth of tumors in mammals and birds and the growth of certain microorganisms. This compound is structurally similar to Mitomycin C (XXII) since both have an aziridine ring fused to a second nitrogen containing ring which is known to act as an alkylating agent.



XXI

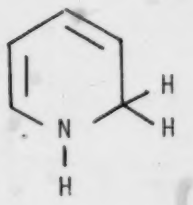


XXII

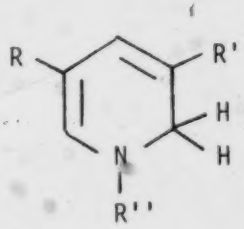
1.2.1.0.0 Physical properties of 1,2-dihydropyridines

Although the parent 1,2-dihydropyridine (XXIII) has not been isolated, stable derivatives XXIV containing electron withdrawing groups at the 1, 3 and 5 positions have been prepared. The resonance interaction of the electron withdrawing groups at the 3 and 5 positions stabilizes 1,2-dihydropyridines by extending the

conjugation. Electron donating groups at the 1, 3 and 5 positions have a destabilizing effect.



XXIII



XXIV

R,R',R'' = $CONH_2$, H,H;
$COOC_2H_5$, $COOC_2H_5$, H;
CN, CN, H; H, H, $COOCH_3$;
H, H, SO_2CH_3
(Some examples of subsituents)

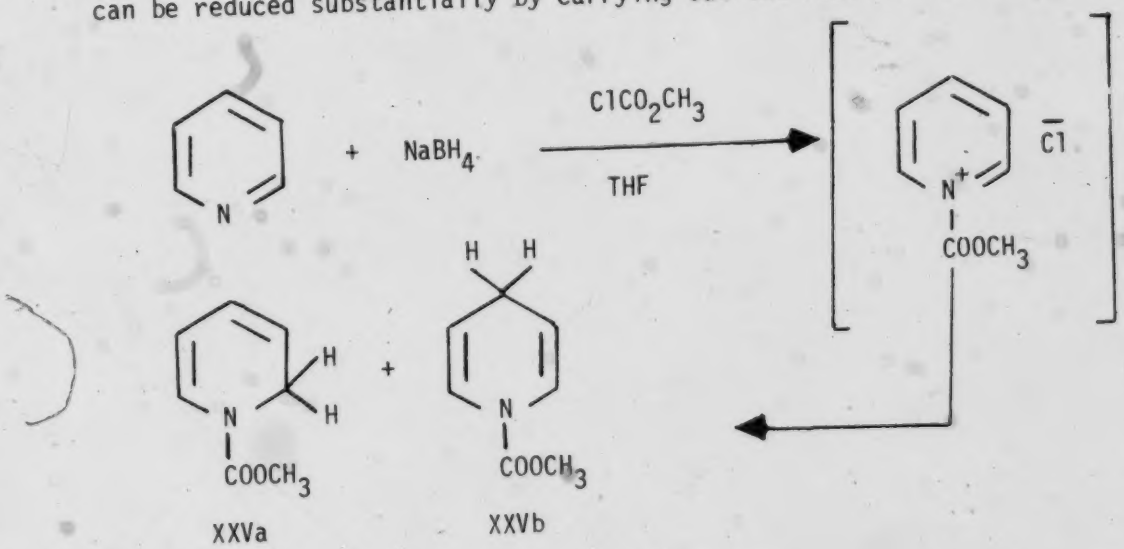
The physical properties of 1,2-dihydropyridines are very characteristic and are most useful in distinguishing them from other isomeric dihydropyridines. The ultraviolet spectra of 1,2-dihydropyridines contain two main bands. The first band appears at 200 - 240 nm and the second at 300 - 400 nm. A third band occuring at 250 - 300 nm is unique to cross-conjugated 1,2-dihydropyridines. The infrared spectra show two characteristic absorptions in the 1500 to 1700 cm^{-1} region due to the C=C stretching modes. N-Unsubstituted 1,2-dihydropyridines also show a NH stretching band between 3100 and 3500 cm^{-1}. The proton resonance spectra of 1,2-dihydropyridines exhibit one low field proton absorption in the 6 to 7 delta region due to C_6-H, three one proton complex multiplets which on occasion are partially overlapped in the 5.75 to 4.25 delta region attributed to the C_4-H, C_3-H and C_5-H respectively and a high field absorption between 4.25 and 3.75 delta due to the C_2-H. This pattern of signals is unique to the 1,2-dihydropyridines.

1.2.2.0.0 Synthesis of some simple 1,2-dihydropyridines

Several reviews[2,3,19,20] are available which include most of the synthetic methods used to prepare 1,2-dihydropyridine derivatives. To avoid an unnecessarily lengthy discussion of the numerous routes employed, only the pertinent synthetic procedures and those closely related will be included.

1.2.2.1.0 Reductions of pyridinium salts with sodium borohydride

Sodium borohydride reduces pyridinium salts and their derivatives to 1,2-dihydropyridines[21,22] which undergo further reduction to tetrahydropyridines unless the hydrogen ion concentration is reduced by addition of alkali[23] or cyanide[24]. Fowler has reported[25] the formation of a mixture of N-methoxycarbonyl-1,2-dihydropyridine (XXVa) and N-methoxycarbonyl-1,4-dihydropyridine (XXVb) on treatment of a pyridine-sodium borohydride mixture with methylchloroformate (eq. 1). The intermediate pyridinium salt is most likely the species reduced by the sodium borohydride. The amount of 1,4-dihydropyridine XXVb can be reduced substantially by carrying out the reaction at -70°C.

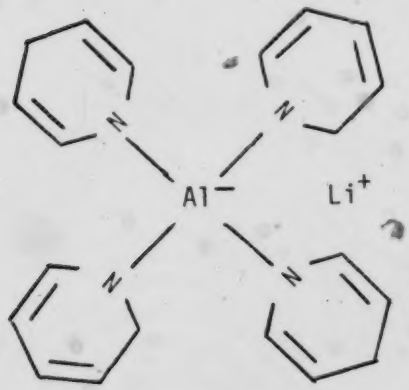


(1)

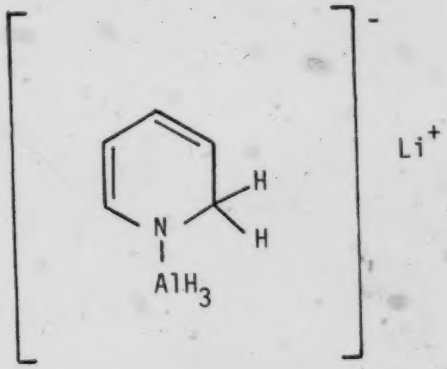
XXVa XXVb

1.2.2.2.0 Reduction of pyridine by lithium aluminum hydride

Treatment of pyridine with lithium aluminum hydride was first reported[26] to produce a highly unstable dihydropyridine product which could not be isolated and characterized. More recent reports[27,28] have shown the structure of the dihydropyridine complex to be lithium-tetrakis-(N-dihydropyridyl)-aluminate (XXVI) rather than the tentatively assigned 1,2-dihydropyridine structure XXVII[29].



XXVI



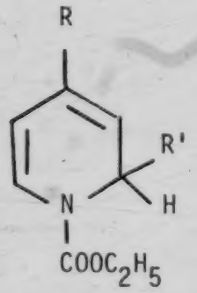
XXVII

1.2.2.3.0 Nucleophilic additions of organometallic reagents to pyridinium salts

The reactions of Grignard reagents with pyridinium salts to prepare 1,2-dihydropyridine derivatives have been studied quite extensively. When the 1,2-dihydropyridine products prepared do not contain electron withdrawing groups, they are usually reacted further without purification due to their instability[30]. Transformation of the products of Grignard reagents and 4-methoxy-1-methyl-pyridinium iodide to their stable dihydropyridine salts has also been accomplished[31].

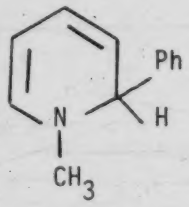
A more recent study has shown that 4-substituted pyridines react with ethylchloroformate and Grignard reagents to produce 2,4-disubstituted-1,2-dihydropyridines XXVIII. These reactions are also believed to proceed via the pyridinium salt. Alkyl and aralkyl 3-cyanopyridinium salts have been reported to form mixtures of 1,2- and 1,6-dihydropyridines on treatment with a Grignard reagent[33]. The reaction of 1,4-dimethylpyridinium iodide with Grignard reagents which afford the corresponding 1,2,4-trisubstituted-1,2-dihydropyridines have also been reported[34].

Organolithium reagents have also been shown to react with pyridinium salts to give the corresponding 1,2-dihydropyridine derivatives. One example[35] is the reaction of phenyllithium with N-methylpyridinium iodide which yields N-methyl-2-phenyl-1,2-dihydropyridine (XXIX).



XXVIII

R,R' = CH_3, n-Bu; CH_3, Ph;
C_2H_5, n-Bu; H, n-Bu



XXIX

1.2.2.4.0 Nucleophilic additions of organometallic reagents to pyridines

Grignard reagents react with pyridines which contain electron withdrawing groups in the 3- and/or 5- positions to produce 1,2- and/or 1,4-dihydropyridines, depending on the substituents at the

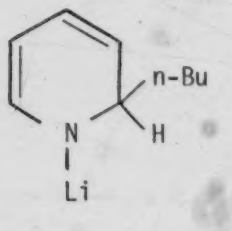
2 and 4 positions. For example, reaction of 3,5-dicyano-2,4-dimethylpyridine with methylmagnesium iodide was shown to yield only 3,5-dicyano-2,4,6-trimethyl-1,2-dihydropyridine while reaction with 3,5-dicyano-2,6-dimethylpyridine produced 3,5-dicyano-2,4,6-trimethyl-1,4-dihydropyridine[36].

Organolithium reagents also react with the similarly substituted pyridines to produce the same products obtained using Grignard reagents except there is a greater tendency for the organolithium reagent to attack the cyano groups. The advantage of organolithium reagents is that substitution on the pyridine ring is not necessary.

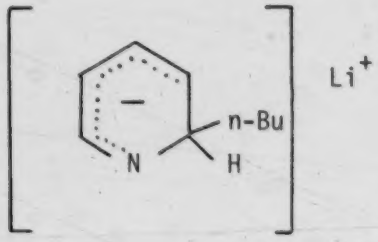
The reactions of organolithium reagents with pyridine was first investigated by Ziegler and Zeiser[37]. These authors reported that n-butyllithium adds to pyridine with subsequent elimination of lithium hydride to give 2-n-butylpyridine.

The postulated intermediate was N-lithio-2-n-butyl-1,2-dihydropyridine (XXX). In later studies[38,39] conclusive evidence was reported which supports the structure of this n-butyllithium pyridine adduct. The proton magnetic resonance data showed increased shielding at the C_3 and C_5 protons indicating that 20% of the negative charge is located at these two positions. The adducts of organolithium reagents and pyridine have also been assigned the sigma (σ) complex structure XXXa. In a related study[40], the isolation and characterization of N-lithio-2-phenyl-1,2-dihydropyridine was reported. The PMR spectrum could be assigned unambiguously to the dihydropyridine structure using the information obtained from spin-spin decoupling experiments and hydrolysis with D_2O. Treatment of the intermediate with dry

oxygen yielded 2-phenylpyridine. A study[41] of the intermediate adducts in the reaction of t-butyllithium with pyridine has also been published.



XXX



XXXa

1.2.3.0.0 Some chemistry of 1,2-dihydropyridines

This discussion will be limited to the pertinent chemical properties of 1,2-dihydropyridine derivatives mentioned in the preceeding sections. The general review[3] on dihydropyridine chemistry can be consulted for the remaining chemical properties.

1.2.3.1.0 Reactions of 1,2-dihydropyridines with complex hydrides

The reduction of 1,2-dihydropyridines with sodium borohydride in aqueous media produces the corresponding 1,2,5,6-tetrahydropyridine derivatives. Initial protonation of the dihydropyridine by a borane-water complex has been shown to be the first step in the reduction[42]. The C=N of the resulting 2,5-dihydropyridinium intermediate is subsequently reduced to give the tetrahydropyridine product.

The reaction of lithium aluminum hydride with N-carbomethoxy-1,2-dihydropyridine has been shown to produce N-methyl-1,2-dihydropyridine which is relatively unstable in comparison to the corresponding 1,4-dihydropyridine isomer[43].

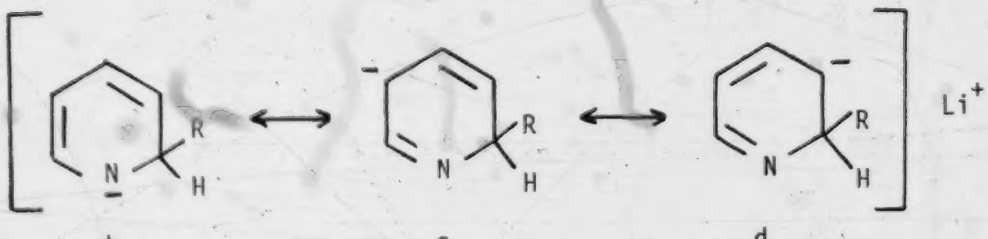
1.2.3.2.0 Reactions of organometallic - pyridine adducts with carbonyls

The reduction of highly electrophilic carbonyl groups using lithium tetrakis-(N-dihydropyridyl)-aluminate (XXVI)[29], the phenyllithium - pyridine adduct[44] and the n-butyllithium - pyridine adduct (XXX)[45,46] have been reported. In general, these dihydropyridyl complexes reduce diaryl ketones most readily, followed by arylalkyl ketones and dialkyl ketones. Carboxylic acids and esters are reported to be essentially inert to the lithium hydride - pyridine complex[29].

1.2.3.3.0 Reactions of organometallic - pyridine adducts with electrophiles

The first reactions of organolithium - pyridine adducts with electrophiles reported gave rise to 2,5-disubstituted pyridines. The resonance structures XXX b-d suggest that these intermediates are capable of undergoing electrophilic attack at the N_1, C_3 and C_5 positions to afford disubstituted pyridines. No product resulting from attack at C_3 has been reported to date.

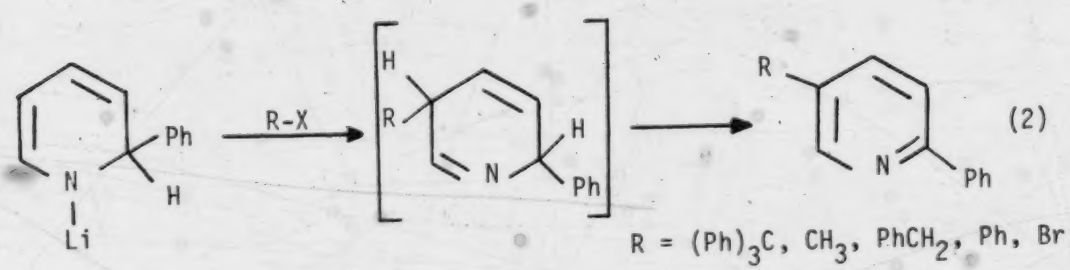
R = Ph, n-Bu



b c d

XXX

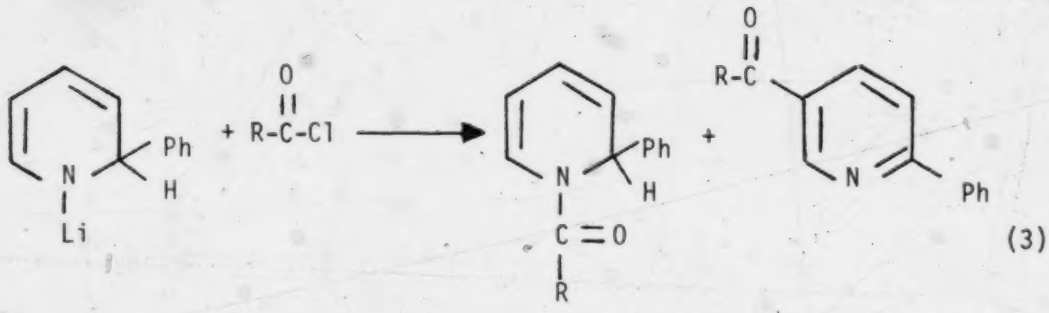
The *in situ* reaction of triphenylmethyl chloride with pyridine and phenyllithium was reported[35] to yield 2-phenyl-5-triphenylmethyl-pyridine in low yield. Much higher yields of 5-benzyl, 5-bromo, 5-methyl and 2,5-diphenylpyridine have been reported[47] from the reaction of isolated N-lithio-2-phenyl-1,2-dihydropyridine with benzyl chloride, bromine, methyl iodide and iodobenzene. The suggested mechanism for the formation of the 2,5-disubstituted pyridines is via a 2,5-disubstituted-2,5-dihydropyridine intermediate as shown in equation 2.



(2)

R = $(Ph)_3C$, CH_3, $PhCH_2$, Ph, Br

A subsequent report describing the reaction of acid chorides and esters with N-lithio-2-phenyl-1,2-dihydropyridine has shown[48] the products to be N-substituted-1,2-dihydropyridines XXXI, C_5-substituted pyridines XXXII and C_5-substituted-1,2-dihydropyridines XXXIII. The oxidized intermediate, 2-phenylpyridine (XXXIV), was also recovered (eq. 3).



(3)

R = CH_3, Ph, CF_3, OC_2H_5

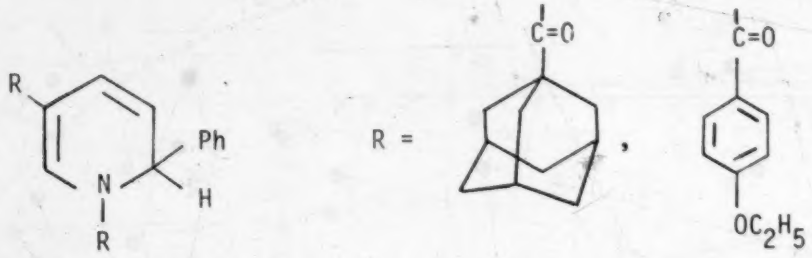
XXXI XXXII

XXXIII XXXIV

Reaction with acetyl chloride and benzoyl chloride gave predominantly N-substitution products XXXI along with low yields of C-substitution products XXXII. A similar reaction using trifluoroacetyl chloride gave primarily XXXIII and XXXII with a trace of XXXI. Ethyl acetate and ethylchloroformate acylated exclusively at nitrogen.

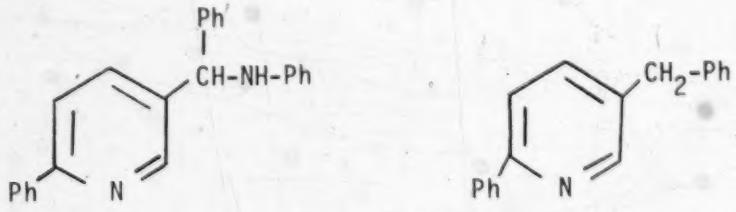
A further study of carbon versus nitrogen substitution using this dienamine system was reported recently[49]. It was shown that the nitrogen to carbon (N/C) substitution ratio was dependent upon the electrophilicity of the acetylating reagent. The less electrophilic acetyl chloride gave N/C substitution in the ratio of 20 to 1. The more electrophilic benzoyl chloride decreased this ratio to 3 to 1 and the highly electrophilic trifluoroacetyl chloride produced a 1 to 16 ratio of N/C substitution products. The reaction of p-ethoxybenzoyl chloride and 1-adamantanecarbonyl chloride with N-lithio-2-phenyl-1,2-dihydropyridine also gave rise to 1,5-disubstituted-2-phenyl-

1,2-dihydropyridines XXXV. The disubstituted-1,2-dihydropyridine XXXV was also isolated from reaction of n-butyl and methyllithium pyridine adduct with methylchloroformate.

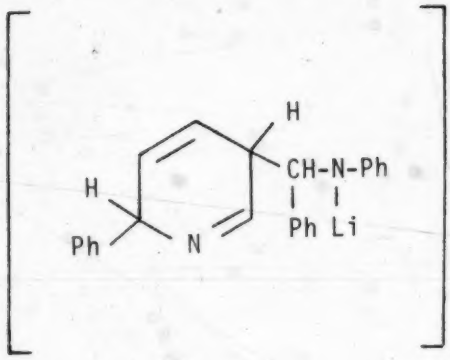


XXXV

A more recent study[50] describes the preparation of 2,5-disubstituted pyridines from reaction of N-lithio-2-phenyl-1,2-dihydropyridine with strong electrophiles. The reaction of Schiff bases was investigated as a method of introducing alkyl amines into the β-position of pyridine. Treatment of the phenyllithium - pyridine adduct with N-benzylideneaniline afforded 2-phenyl-5-(α-anilinobenzyl) pyridine (XXXVI) and 2-phenyl-5-benzylpyridine (XXXVII), as well as N-benzylaniline and 2-phenylpyridine. The mechanism postulated for the formation of XXXVII involves aromatization of the intermediate 2,5-dihydropyridine XXXVIII followed by hydride attack and elimination of anilide anion to yield XXXVII.

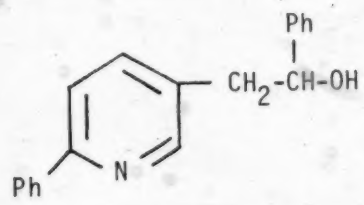


XXXVI XXXVII

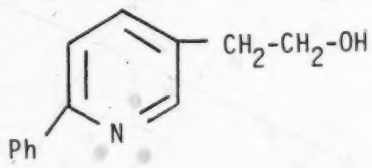


XXXVIII

The reactions of styrene oxide and ethylene oxide with N-lithio-2-phenyl-1,2-dihydropyridine afforded 2-(2-phenyl-5-pyridyl)-1-phenyl-ethanol (XXXIX) and 2-(2-phenyl-5-pyridyl)-ethanol (XL) respectively.

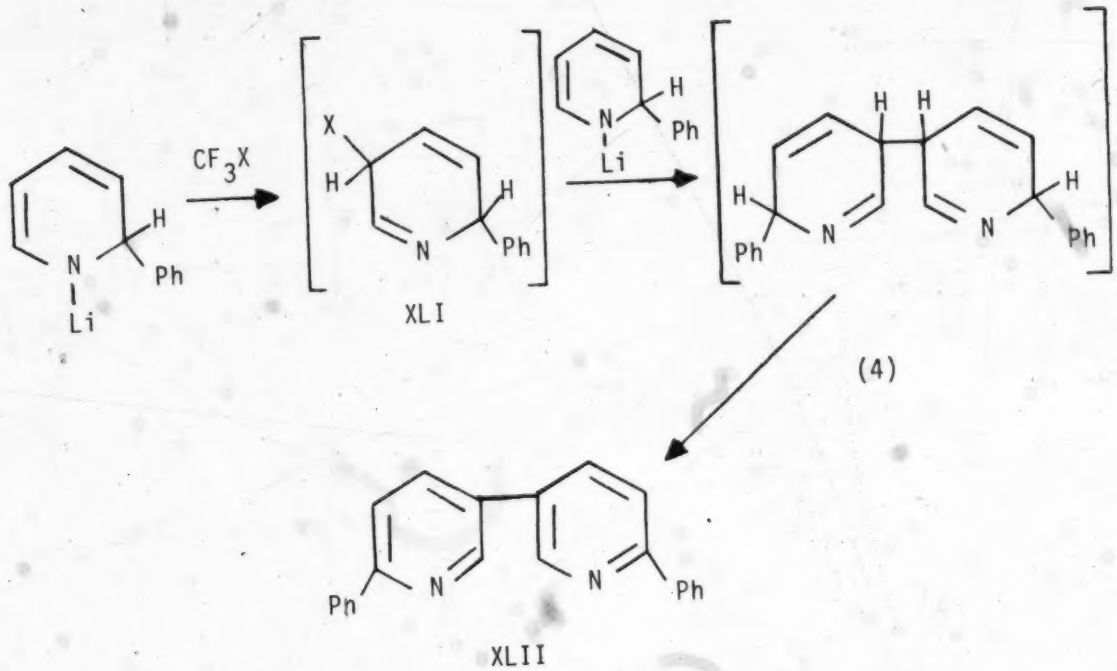


XXXIX



XL

The reactions of trifluoromethyl iodide and bromide with N-lithio-2-phenyl-1,2-dihydropyridine did not yield any of the expected 5-trifluoromethyl-2-phenylpyridines but did give rise to 6,6'-diphenyl-3,3'-dipyridyl (XLII). The mechanism postulated involves attack of 5-halo-2,5-dihydropyridine intermediate XLI by a second N-lithio-2-phenyl-1,2-dihydropyridine molecule with subsequent aromatization as shown in equation 4. The reaction of N-bromosuccinimide also yielded the dimer XLII.

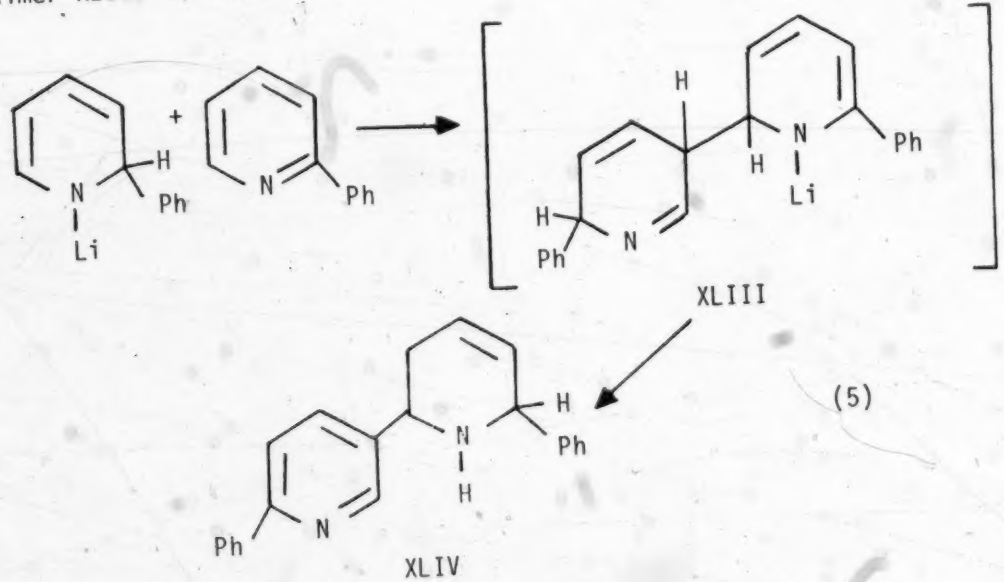


XLI

XLII

(4)

The reaction of 2-phenylpyridine with N-lithio-2-phenyl-1,2-dihydropyridine gave rise to the unexpected 6,6'-diphenyl-1,2,3,6-tetrahydro-2,3'-dipyridyl (XLIV). The mechanism proposed for the formation of XLIV involves disproportionation of the dihydropyridyl dimer XLIII as shown in equation 5.

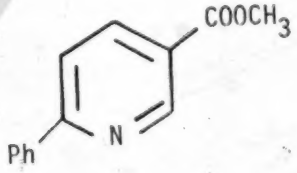


XLIII

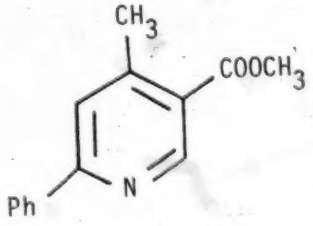
XLIV

(5)

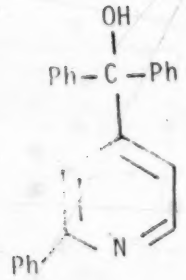
A method for the arylation-carboxylation of pyridine and 4-picoline has been reported[51]. Treatment of pyridine or 4-picoline with phenyllithium, carbon dioxide and then diazomethane yielded the corresponding methyl esters of 2-phenylpyridine-5-carboxylic acid (XLV) and 2-phenyl-4-methylpyridine-5-carboxylic acid (XLVI). In view of their results, the product from reaction of benzophenone with N-lithio-2-phenyl-1,2-dihydropyridine initially reported[44] was reinvestigated. The compound earlier assigned[44] structure XLVII was shown to be the corresponding 2,5-disubstituted isomer XLVIII. Further confirmation was provided by comparison to the product obtained from treatment of their methyl ester XLV with an excess of phenyllithium. The 2-phenyl-5-diphenylhydroxymethylpyridine (XLVIII) is in agreement with the corresponding 2-n-butyl compound prepared by Levine and Kadunce[46].



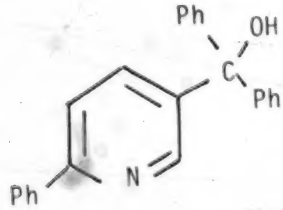
XLV



XLVI

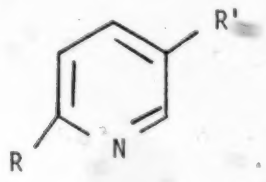


XLVII



XLVIII

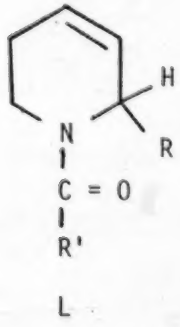
The use of methyllithium- and phenyllithium - pyridine adducts to prepare the corresponding 5-thiopyridines has recently been investigated[52]. Preparation of 2-methyl- or 2-phenyl-5-methylthio-, butylthio- or phenylthiopyridines XLIX using the appropriate organolithium and disulfide compounds has been accomplished.



XLIX

R,R' = Ph, SCH_3; Ph, Sn-bu; Ph, SPh; CH_3, Sn-bu; CH_3, SPh

Treatment of organolithium pyridine adducts such as N-lithio-2-phenyl (butyl)-1,2-dihydropyridines with one equivalent of water yields the corresponding 2-substituted-1,2-dihydropyridines[38]. These 2-substituted-1,2-dihydropyridines react with acetyl and sulfonyl chlorides similar to organolithium pyridine adducts to yield N-substituted and/or C-substituted products[53] along with N-substituted-1,2,5,6-tetrahydropyridine derivatives L.



L

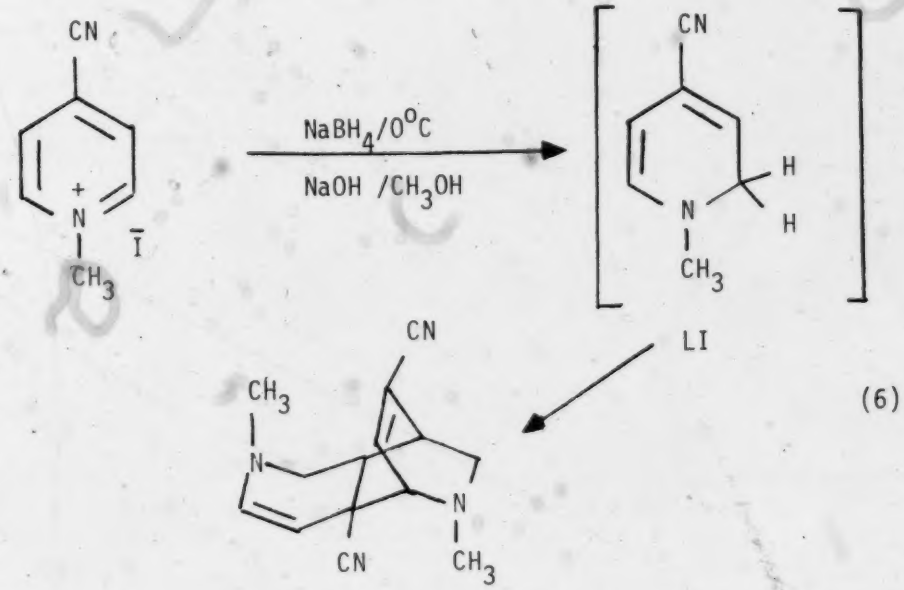
R,R' = Ph, CH_3; n-Bu, CH_3; Ph, Ph,; Ph, 1-adamantyl

Lithium tetrakis-(N-dihydropyridyl)-aluminate (XXVI)[28], prepared

from lithium aluminum hydride and pyridine, on reaction with electrophilic reagents is a novel and efficient reaction to prepare 3-substituted pyridines[54]. Treatment of XXVI with an alkyl halide, benzyl chloride or bromine yielded the corresponding 3-methyl-, 3-ethyl-, 3-benzyl- and 3-bromopyridines in high yield.

1.2.3.4.0 Some cycloaddition reactions of 1,2-dihydropyridines

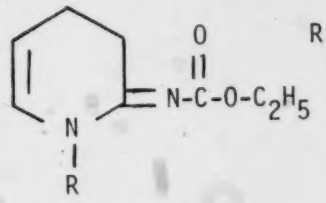
The most common cycloaddition reaction of the 1,2-dihydropyridines is the Diels-Alder reaction. Dienophiles which have been reacted with 1,2-dihydropyridines include maleic anhydride[55], N-phenylmaleimide[23], methyl vinyl ketone[56] and acrylonitrile[57]. One study[58] has postulated that the sodium borohydride reduction of a pyridinium salt in an alkaline medium stops at the 1,2-dihydropyridine derivative LI and subsequently undergoes the Diels-Alder cycloaddition with one molecule acting as the diene and another as the dienophile (eq. 6).



(6)

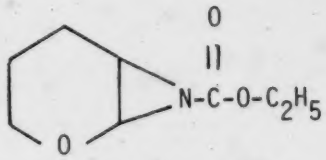
A recent investigation[59] describing the reaction of N-substituted-1,2-dihydropyridines with 1,2,4-triazoline-3,5-diones and maleimides has shown the Diels-Alder cycloaddition to proceed stereospecifically to afford endo cycloaddition products.

A brief report[60] of the reaction of ethylazidoformate with 1,4-dihydropyridines to produce the corresponding 2-carboethoxyimino-1,2,3,4-tetrahydropyridines LII suggested that mechanistically, a 1,3-dipolar cycloaddition followed by collapse of triazole and aziridine intermediates occurs. Neither intermediate was isolated. This study paralleled the photochemical reaction of ethylazidoformate with dihydropyran which afforded 7-carboethoxy-7-aza-2-oxabicyclo [4.1.0] heptane[61] (LIII).



R = H, Ph

LII



LIII

1.2.4.0.0 Some 1,3-dipolar cycloaddition reactions

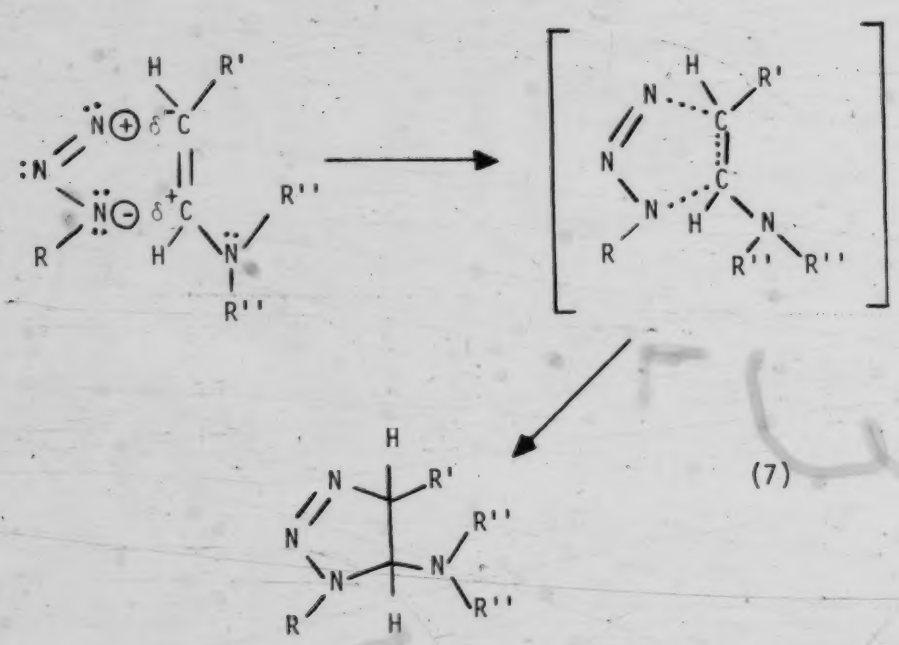
Several authors have reviewed the chemistry of 1,3-dipolar cycloaddition reaction in detail[62,63]. The following general discussion will be limited to pertinent aspects involving; the type of dipole and dipolarophiles, the stereoselectivity of the reaction, the stability of the products and the controlled decompostion products.

Some of the more common 1,3-dipoles studied include; nitrile

ylides, nitrile imines, nitrile oxides, diazoalkanes, azides, azomethine ylides, azomethine imines, carbonyl imines and carbonyl ylides. All react by the characteristic 1,3-dipolar cycloaddition mechanism to produce five membered rings of varying stabilities. Reactions involving organic azides have been reviewed in a general context[64,65] as well as aspects of structure and reactivity[66].

Many types of dipolarophiles have been employed in cycloaddition reactions. Numerous examples of compounds containing the imine, carbonyl, alkene or alkyne functional groups have been studied. The most common system investigated is the carbon-carbon double bond. The reactivity of the alkenes used may be altered by the functionality present in the molecule. Compounds which contain strained ring systems are more reactive. Conjugation with nitrogen as in the enamine system gives rise to an electron-rich dipolarophile which is more reactive. The presence of adjacent electron withdrawing groups as in an anhydride will yield an electron-deficient dipolarophile which is also highly reactive.

The concerted mechanism by which the two new sigma (σ) bonds are formed results in a stereoselective "cis" addition. The organic azides however, can add to asymetric dipolarophiles in either direction. In the absence of steric effects, the product is determined by electronic effects. In general, the enamine undergoes nucleophilic attack at the α-carbon by the azide nitrogen containing the substituent and electrophilic attack at the β-carbon by the terminal azide nitrogen (see eq. 7). Examples of these will be given in the following sections.



(7)

It has also been shown[67] that electron rich double bonds react more readily with azides carrying electron withdrawing substituents and vice versa. This can be attributed to a partially charged transition state.

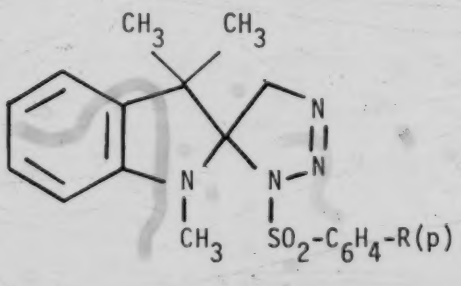
The stability of the triazolinic ring system depends primarily on the substituent attached to nitrogen. When the group is electron withdrawing, the ring system is quite labile.

Thermal decomposition of triazolines leads to aziridines, imines or a mixture. It has been shown[68] that linear and simple cyclic triazolines decompose by loss of nitrogen primarily to the imines while highly substituted and polycyclic triazolines yield mainly aziridines. Photochemical decomposition of triazolines leads almost exclusively to the corresponding aziridines.

1.2.4.1.0 Reactions of organic azides and enamines

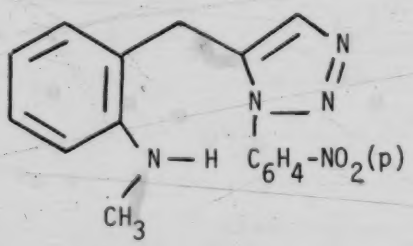
A study demonstrating the orientation of the addition product obtained from reaction of an enamine with an organic azide was reported by Monk and Kim[69] in 1964. More recently, a ring contraction procedure was developed which employed the reaction of cyanogen azide with the enamine of a cyclic ketone[70]. This ring contraction reaction involved loss of nitrogen followed by a rearrangement. Studies[71] have also been reported for reaction of cyclic enamines with substituted-phenyl azides and benzoyl azide.

A more recent investigation[72] has shown that 1,3,3-trimethyl-2-methylene indole reacts with sulfonyl and aryl azides to produce triazoline intermediates. The unstable sulfonyl triazolines LIV rapidly undergo decomposition to the sulfonimide and diazomethane. One of the stable phenyl triazolines could be isomerized using base to produce a stable triazole LV.



R = CH_3, OCH_3, NO_2

LIV



LV

The reactions of p-bromophenyl azide with the dienamine trans-1-diethylamino-1,3-butadiene has been reported[73] to yield adducts

where addition has occurred at the C_1-C_2 double bond and at both the C_1-C_2 and C_3-C_4 double bonds. Treatment of these triazoline with base also afforded the stable triazoles.

2.0.0.0.0 OBJECTS OF RESEARCH

Reactions of organolithium reagents with pyridine have been reported to yield N-lithio-2-substituted-1,2-dihydropyridines[36-41]. Treatment of these organolithium - pyridine adducts with alkyl, aralkyl and aryl halides afforded 2,5-disubstituted pyridines[47]. More recently, studies involving carbon versus nitrogen acylation of organolithium - pyridine adducts with acid chlorides and esters have been published[48,49]. The introduction of alkyl groups containing functional moieties into the C-5 position has also been reported[50]. It was therefore of interest to extend the scope of this reaction by reacting the appropriate electrophiles with organolithium - pyridine adducts to introduce the desired functionality at the C-5 and/or N-1 positions. The products obtained from these reactions would be 2,5-disubstituted pyridines and/or N-substituted-1,2-dihydropyridines.

N-substituted-1,2-dihydropyridines undergo the Diels-Alder cycloaddition reaction with dienophiles[55-59]. It was therefore of interest to study the reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with the N-substituted-1,2-dihydropyridines to be synthesized.

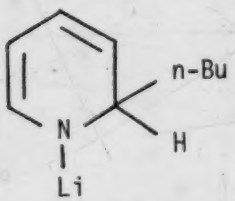
The 1,3-dipolar cycloaddition reaction of 1,4-dihydropyridines with ethyl azidoformate has been investigated[60]. More recently, the reaction of aryl azides with an acrylic dienamine has been reported[73]. To date there has been no report describing a 1,3-dipolar cycloaddition reaction involving a 1,2-dihydropyridine. It was therefore of interest to study the reaction of organic azides with a series of N-unsubstituted- and N-substituted-1,2-dihydropyridines.

3.0.0.0.0 DISCUSSION

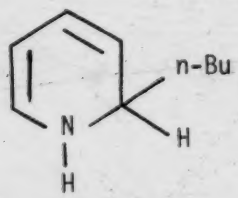
3.1.0.0.0 Reactions of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and 2-n-butyl-1,2-dihydropyridine (LVI) with electrophiles

N-Lithio-2-n-butyl-1,2-dihydropyridine (XXX) was generated *in situ* by addition of n-butyllithium to a solution of pyridine in anhydrous ether under a nitrogen atmosphere at $0^{o}C$. This solution was cooled to $-77^{o}C$ and the appropriate electrophile was added.

2-n-Butyl-1,2-dihydropyridine (LVI) was obtained from XXX by adding one equivalent of water at $0^{o}C$. The solution was then warmed to $25^{o}C$ and the appropriate electrophile was added.



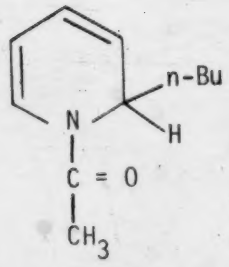
XXX



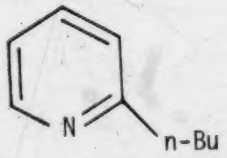
LVI

3.1.1.0.0 Synthesis of N-substituted-1,2-dihydropyridines

The reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) with ethyl acetate afforded N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) (99%) and 2-n-butylpyridine (LVIII) (0.82%). The absence of 2-n-butyl-5-acetylpyridine resulting from C-acetylation is consistent with the previous observation that reaction of N-lithio-2-phenyl-1,2-dihydropyridine with weak electrophiles gave predominantly N-acylation[49].



LVII

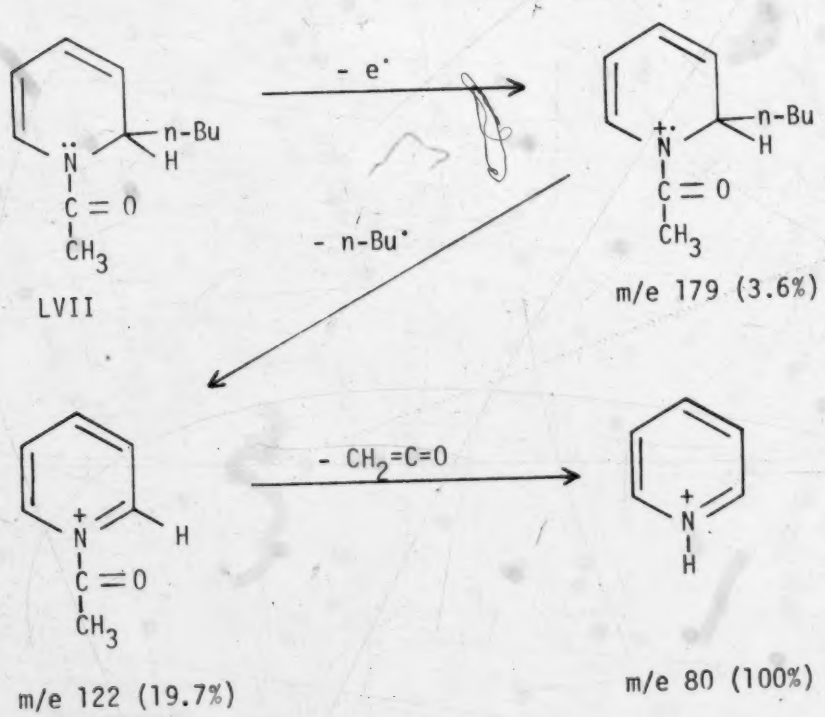


LVIII

The structure of N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) was consistent with its infrared (ir), nuclear magnetic resonance (nmr) and mass spectra (ms). The infrared spectrum of this compound displayed peaks at 1665 cm^{-1} due to the carbonyl group and at 1650 and 1635 cm^{-1} attributed to the two carbon-carbon double bonds of the dienamine system. The nmr spectrum (δ) in deuterochloroform exhibited a 3 H triplet (J = 7 Hz) at 0.9 due to the terminal methyl of the n-butyl group, a 6 H multiplet at 1.1 to 1.9 attributed to the three methylenes of the n-butyl group, a 3 H singlet at 2.19 due to the acetyl methyl, a 1 H multiplet at 5.07 due to C_2-H, a 1 H multiplet at 5.33 attributed to C_5-H, a 1 H multiplet at 5.67 due to C_3-H, a 1 H multiplet at 5.82 due to C_4-H and a 1 H multiplet ($J_{5,6}$ = 7.5 Hz) at 6.5 due to C_6-H. The mass spectrum exhibited a molecular ion at m/e 179 (M^+ Calcd. for $C_{11}H_{17}NO$: 179.1310; Found: 179.1310). The molecular ion undergoes loss of the n-butyl group to produce a peak at m/e 122 ($C_7H_8NO^+$). Further loss of ketene gives rise to the base peak at m/e 80 ($C_5H_6N^+$) as shown in Scheme 1.

Scheme 1

Fragmentation of N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII)



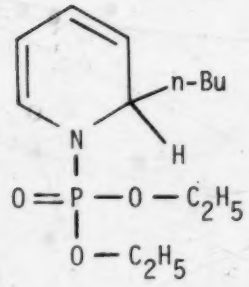
LVII

m/e 179 (3.6%)

m/e 122 (19.7%)

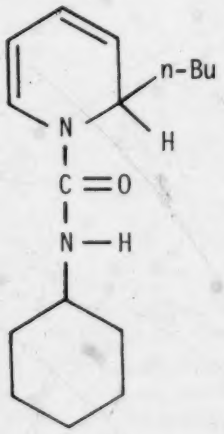
m/e 80 (100%)

Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) with diethylchlorophosphate afforded N-diethylphosphoryl-2-n-butyl-1,2-dihydropyridine (LIX) (68.3%). No C-substituted product was detected by thin layer chromatography (tlc). The structure assigned to LIX is consistent with its infrared, nmr and mass spectra. Treatment of 2-n-butyl-1,2-dihydropyridine (LVI) with diethylchlorophosphate in the presence of triethylamine afforded LIX (16.8%) and 2-n-butyl-pyridine (LVIII) (8.9%).

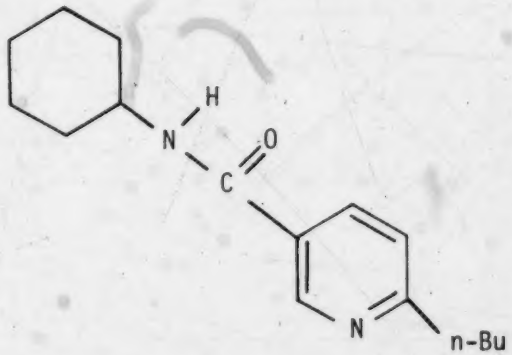


LIX

The reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) with cyclohexylisocyanate afforded N-(N-cyclohexyl)carboxamido-2-n-butyl-1,2-dihydropyridine (LX) (17%) and 5-(N-cyclohexyl)carboxamido-2-n-butylpyridine (LXI) (14%). The structures assigned to LX and LXI are consistent with their infrared, nmr and mass spectra.



LX



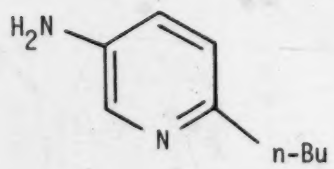
LXI

3.1.2.0.0 Synthesis of 2,5-disubstituted pyridines

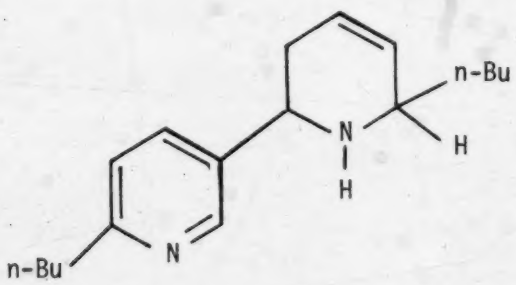
The reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) with other electrophiles was investigated as a method to prepare

β-substituted pyridines. The presence of N-substituted-1,2-dihydropyridines in these reactions could not be detected by tlc. All of the structures assigned to the compounds prepared are consistent with their infrared, nmr and mass spectra.

Treatment of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) with one equivalent of chloramine afforded 2-n-butylpyridine (LVIII) (7.9%), 2-n-butyl-5-aminopyridine (LXII) (23%) as well as the unexpected 6,6'-di-n-butyl-1,2,3,6-tetrahydro-2,3'-dipyridyl (LXIII) (36.1%). The reaction of three equivalents of XXX with chloramine yielded LVIII (2.7%), LXII (57.4%) and LXIII (30.3%). The tetrahydro product LXIII is believed to arise from the reaction of XXX with LVIII (some of which is always obtained) in view of the known reaction of N-lithio-2-phenyl-1,2-dihydropyridine with 2-phenylpyridine[50].



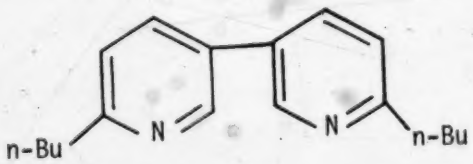
LXII



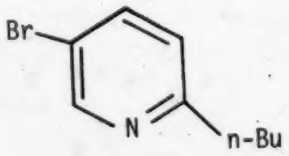
LXIII

The reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) with cyanogen bromide effected by adding one equivalent of cyanogen bromide to XXX afforded 2-n-butylpyridine (LVIII) (22%) and 6,6'-di-n-butyl-3,3'-dipyridyl (LXIV) (26.4%). The formation of LXIV

probably arises as a result of the reaction of XXX with 2-n-butyl-5-bromo-2,5-dihydropyridine and subsequent aromatization. This mechanism is similar to that proposed for the reaction of N-lithio-2-phenyl-1,2-dihydropyridine with trifluoromethyl halides[50]. The reaction of 2-n-butyl-1,2-dihydropyridine (LVI) with cyanogen bromide also afforded LVIII (27.1%) and LXIV (7.2%). An inverse addition procedure was employed using a large excess of cyanogen bromide to prevent the formation of LXIV. Thus, addition of one equivalent of XXX to five equivalents of cyanogen bromide gave rise to 2-n-butylpyridine (32.5%) and 2-n-butyl-5-bromopyridine (LXV) (14.9%). Similarly, addition of XXX to excess N-bromosuccinimide afforded LVIII (8.2%) and LXV (10.5%). The presence of LXIV in these two reactions could not be detected by tlc.



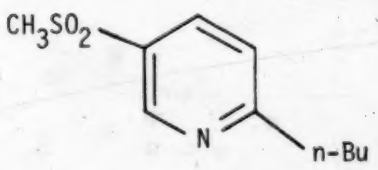
LXIV



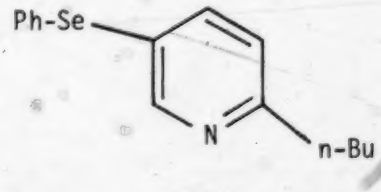
LXV

The reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) with N-methanesulfonylpyridinium chloride was studied as a method to prepare β-alkylsulfonyl pyridines. However, reaction of XXX with N-methanesulfonylpyridinium chloride afforded 2-n-butylpyridine (LVIII) (20%) and the unexpected 6,6'-di-n-butyl-3,3'-dipyridyl (LXIV) (6.9%). When 2-n-butyl-1,2-dihydropyridine (LVI) was allowed to react with N-methanesulfonylpyridinium chloride 2-n-butylpyridine (LVIII) (39.8%) and 2-n-butyl-5-methanesulfonylpyridine (LXVI) (11.2%) were obtained.

In a related study it was shown that reaction of LVI with methanesulfonyl chloride affords a mixture of LXVI and N-methanesulfonyl-2-n-butyl-1,2,5,6-tetrahydropyridine[53].



LXVI



LXVII

The reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) with phenylselenyl chloride yielded 2-n-butylpyridine (LVIII) (12.2%) and 2-n-butyl-5-phenylselenylpyridine (LXVII) (16.3%). Similarly, the reaction of 2-n-butyl-1,2-dihydropyridine (LVI) with phenylselenyl chloride afforded LVIII (13.4%) and LXVII (17.8%).

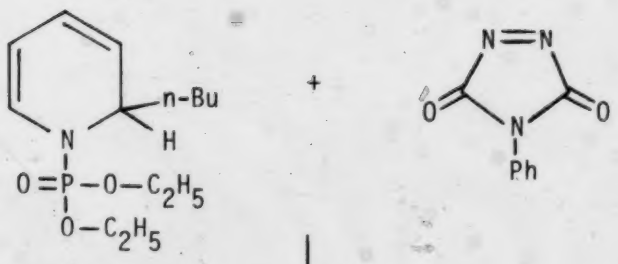
The introduction of a methyl substituent into the C-5 position was also investigated. The reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) with methyl-p-toluenesulfonate afforded 2-n-butylpyridine (LVIII) (7.9%) and 2-n-butyl-5-methylpyridine (LXVIII) (54.7%). Treatment of 2-n-butyl-1,2-dihydropyridine (LVI) with methyl-p-toluenesulfonate yielded LVIII (14.8%) and LXVIII (16.1%). Similarly, reactions of XXX with methyl trifluoromethanesulfonate gave LVIII (5.3%) and LXVIII (42.7%) while LVI afforded LVIII (16.4%) and LXVIII (19.7%).

The infrared, nmr and mass spectra for LXVIII are identical to those exhibited by 2-n-butyl-5-methylpyridine obtained from the reaction of methyl iodide with N-lithio-2-n-butyl-1,2-dihydropyridine[47].

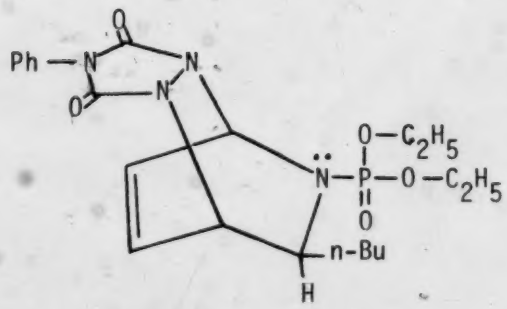
3.2.0.0.0 Diels-Alder cycloaddition of N-phenyl-1,2,4-triazoline-3,5-dione with a N-substituted-1,2-dihydropyridine

A recent report[59] describing the facile Diels-Alder cycloaddition of N-substituted-1,2-dihydropyridines with the highly reactive 1,2,4-triazoline-3,5-diones prompted study on a wider variety of N-substituted-1,2-dihydropyridines. For example, reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with N-diethylphosphoryl-2-n-butyl-1,2-dihydropyridine (LIX) afforded 5-endo-diethylphosphoryl-6-exo-n-butyl-2,3,5-triaza-bicyclo [2.2.2] oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide (LXIX) (97%). The mechanism of this reaction involves the ($\pi 2 + \pi 4$) cycloaddition of 4-phenyl-1,2,4-triazoline-3,5-dione to the less hindered face of LIX to form the endo-adduct LXIX. The stereochemistry of the diethylphosphoryl and n-butyl groups were assigned on the basis of the nmr spectral evidence. The C_6-H and diethylphosphoryl protons are deshielded relative to that of the fully saturated compounds indicating that the diethylphosphoryl group is endo and the n-butyl group is exo. The steric bulk of the diethylphosphoryl group likely prevents addition from the hindered face to give the exo-cycloaddition product.

The structure assigned to LXIX is consistent with its infrared, nmr and mass spectra. A detailed discussion of the spectral data was presented in a recent report[59].



LIX



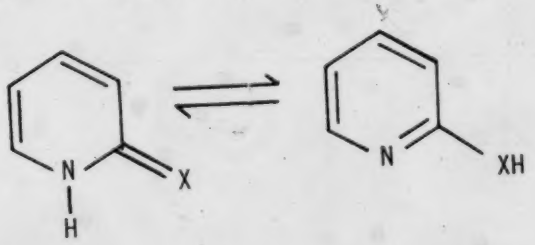
LXIX

3.3.0.0.0 Reactions of organic azides with pyridines and 1,2-dihydropyridines

Organic azides undergo 1,3-dipolar cycloaddition reactions at low temperatures whereas, at elevated temperatures they decompose to nitrenes which then undergo substitution reactions. All the reactions described in this study were effected at temperatures below the decomposition temperatures of the azides employed[64,74]. The mechanism of the 1,3-dipolar cycloaddition was included in the introduction. Specific points involving stereochemistry and selectivity will be repeated in the discussion of subsequent reactions.

3.3.1.0.0 Reactions of cyanogen azide with pyridines

Pyridines possessing hydroxyl, mercapto or amine functionality at the C_2 - position (LXXb) exist in tautomeric equilibrium with the corresponding 1,2-dihydropyridines (LXXa) which contain a cyclic dienamine system. It was therefore of interest to study the 1,3-dipolar cycloaddition reaction of cyanogen azide with LXXa as a method to prepare novel bicyclic compounds with potential pharmacological activity.



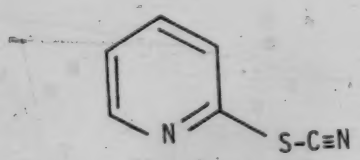
X = O, S, NH

LXXa LXXb

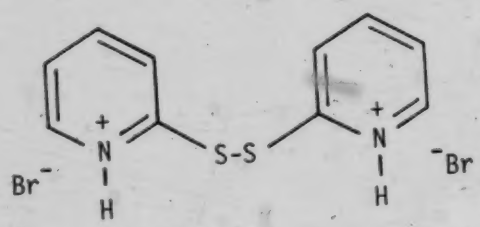
The reaction of cyanogen azide with 2-pyridone for 48 hours at 25° failed to proceed and starting materials were recovered. In contrast, reaction of 2-mercaptopyridine with cyanogen azide afforded the unexpected 2-pyridylthiocyanide (LXXI) (53.6%) and 2,2'-dithiodipyridyl dihydrobromide (LXXII) (44.5%). The formation of LXXII suggests that the preparation of cyanogen azide using equimolar amounts of cyanogen bromide and sodium azide was incomplete. The reaction of cyanogen bromide with 2-mercaptopyridine was therefore investigated and was also found to afford the dipyridyl salt (LXXII) (96.3%) and LXXI (3.4%). The formation of LXXI probably arises from nucleophilic displacement of azide and bromide ions from cyanogen azide and cyanogen

bromide respectively as a result of nucleophilic attack by 2-mercapto-pyridine.

The structure assigned to LXXII is consistent with its infrared and nuclear magnetic resonance spectra and elemental analysis. Treatment of LXXII with base afforded 2,2'-dithiodipyridyl which exhibited spectral data identical to those of an authentic sample.



LXXI



LXXII

The reaction of 2-mercaptopyridine-N-oxide with cyanogen azide afforded two products which were not characterized or investigated further. The nmr spectra indicated that both were 2-substituted pyridines however, the mass spectra were inconsistent with any type of dithiodipyridyl-N-oxide structure.

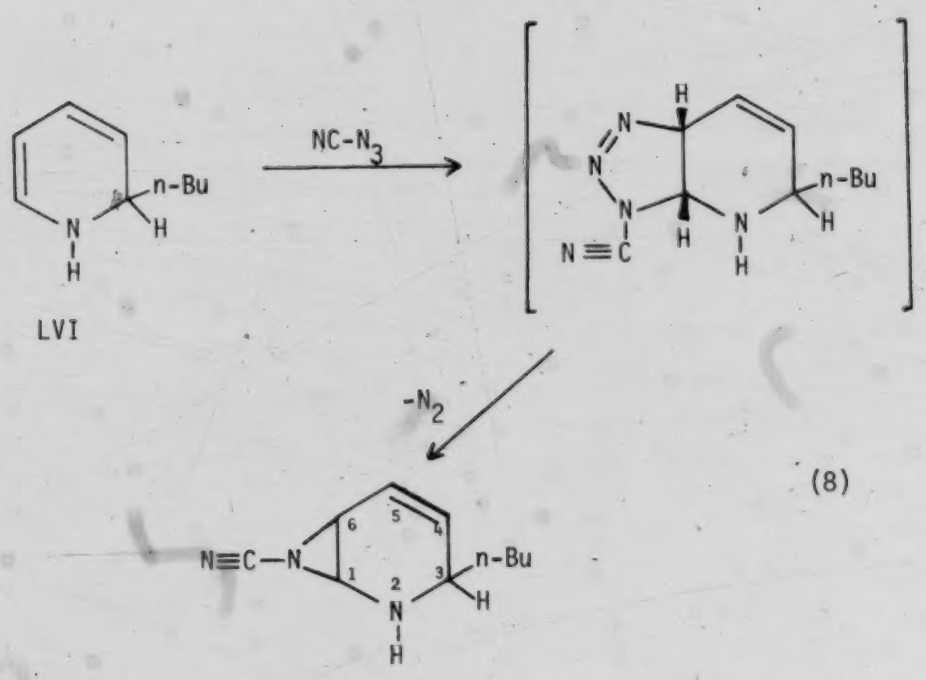
3.3.2.0.0 Reactions of organic azides with 1,2-dihydropyridines

The following discussion involves a number of reduced pyridine compounds possessing exocyclic nitrogen subsituents. The method of nomenclature used will follow that of Chemical Abstracts. The compound is named as an amine derivative. The cycloketonic group is then named as an ylidene and the position of attachment on the ring is indicated by the number following it.

3.3.2.1.0 Reactions of cyanogen azide with 1,2-dihydropyridines

The preparation of 2-substituted-1,2-dihydropyridines by hydrolysis of 2-substituted-N-lithio-1,2-dihydropyridines with one equivalent of water also produces one equivalent of lithium hydroxide. Although most of the lithium hydroxide rapidly precipitates out of anhydrous ether or tetrahydrofuran, a small amount remains suspended in the solvent. An assay of the supernatant has shown the presence of 5% lithium hydroxide. The suspended lithium hydroxide can be removed completely if an excess of water is added followed by drying with anhydrous sodium sulfate.

The reaction of 2-n-butyl-1,2-dihydropyridine (LVI) (lithium hydroxide free) with cyanogen azide afforded 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII) in quantitative yield. The most probable mechanism for this reaction involves the formation of an unstable triazoline intermediate via a 1,3-dipolar cycloaddition reaction at the C_5-C_6 olefinic bond (eq. 8). If the triazoline intermediate is a product of electronic control, the nitrogen atom bearing the cyano group should be directed to the carbon of the enamine bond bearing the enamine ring nitrogen[64]. Evolution of nitrogen at 0^o indicated the facile decomposition of the intermediate triazoline. It has been shown that the triazolines of strained cyclic olefins decompose to primarily aziridine products[68]. The resultant product in this case is the bicyclic structure LXXIII. Although addition may occur at either the C_3-C_4 and/or C_5-C_6 olefinic bonds, no addition product other than LXXIII was detected.



LVI

(8)

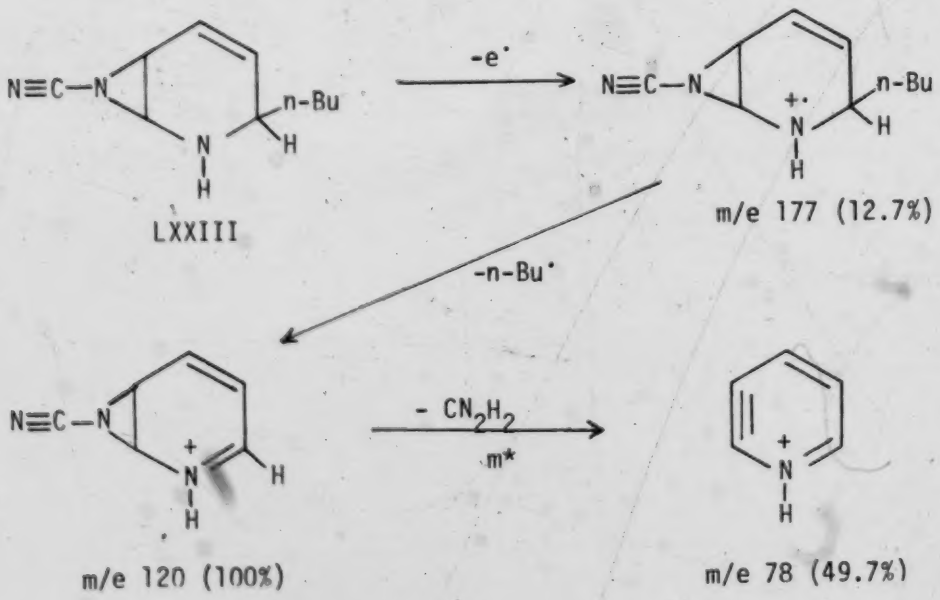
LXXIII

The infrared spectrum of LXXIII showed the presence of an olefinic bond (1605 cm^{-1}), a cyano group (2180 cm^{-1}) and a secondary amine (3225 cm^{-1}). The nmr spectrum (δ) exhibited a distorted 3 H triplet (J = 7 Hz) at 0.9 due to the terminal methyl, a 6 H multiplet at 1.1 - 1.9 due to the three methylenes, a complex 2 H multiplet at 3.25 attributed to the C_1-H and C_6-H, a 1 H multiplet at 4.17 due to the C_3-H, the characteristic 2 H multiplet present in 1,2,3,6-tetrahydropyridines[53,75] at 5.8 due to C_4-H and C_5-H and a broad 1 H singlet at 8.63 attributed to the NH which exchanges with deuterium oxide. The high field position of C_1-H and C_6-H can be attributed to the electron rich aziridine ring system. The nmr spectrum did not indicate

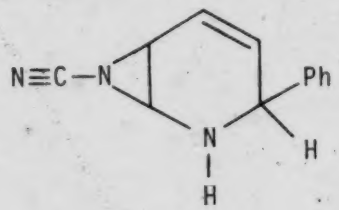
stereoisomerism about the C-1 and C-6 positions however, the possibility that the C_1-H and C_6-H in the two stereoisomers would exhibit chemical equivalence cannot be excluded. A product resulting from addition to the C_3-C_4 olefinic bond is not consistent with the nmr spectral data. The mass spectrum of LXXIII exhibited a molecular ion at m/e 177 (M^+ Calcd. for $C_{10}H_{15}N_3$: 177.1266; Found: 177.1265). The major fragmentation pathway as shown in Scheme 2 involves the loss of the n-butyl group to produce the base peak at m/e 120 ($C_6H_6N_3^+$) which in turn fragments by loss of cyanoamine to produce a peak at m/e 78 ($C_5H_4N^+$).

Scheme 2

Major fragmentations of 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII)

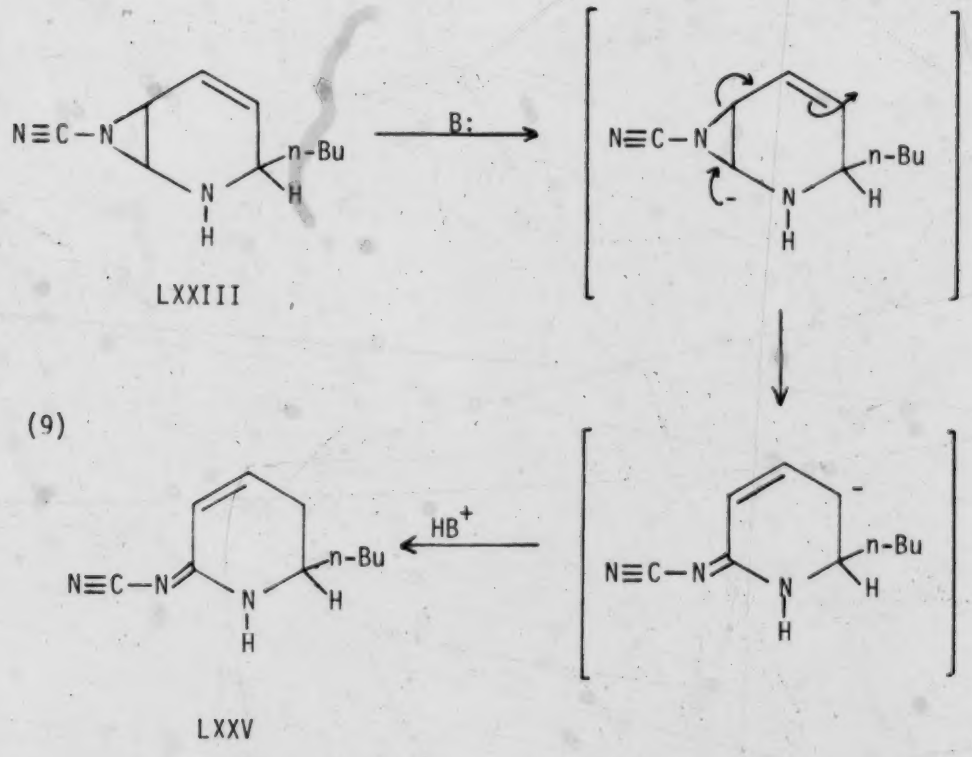


The reaction of 2-phenyl-1,2-dihydropyridine with cyanogen azide under the same reaction conditions yielded 3-phenyl-7-cyano-2,7-diaza-bicyclo [4.1.0] hept-4-ene (LXXIV) in quantitative yield. The assigned structure is in agreement with its infrared, nmr and mass spectra as well as the spectral data exhibited by the corresponding 2-n-butyl compound (LXXIII) previously discussed.



LXXIV

In the reactions just described, the presence of the isomeric alkylidene cyanamides were not detected. However, chromatography of LXXIII on a neutral alumina (Brockman Activity I) column gave a product which exhibited spectral data consistent with 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXV) (79%). One possible mechanism for the formation of the isomeric LXXV may involve initial abstraction of the active C_1-H of LXXIII followed by opening of the aziridine ring with a shift of the olefinic bond.



LXXIII

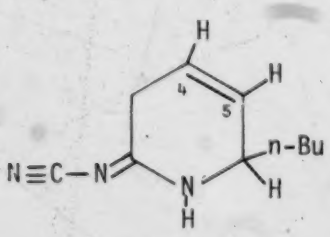
(9)

LXXV

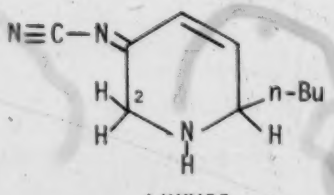
Further evidence in support of this mechanism is the observation that triethylamine is also capable of catalysing this reaction. On the other hand, chromatography of LXXIII on an acidic alumina (Brockman Activity I) column yielded only 7.7% of LXXV and 92.3% of LXXIII. The relative amounts were calculated from nmr spectrum of the mixture using the integrals of C_3-H for LXXIII and C_6-H for LXXV.

The structure of compound LXXV was assigned on the basis of its uv, ir, nmr and mass spectra. The ultraviolet spectrum showed two bands at 242 and 288 nm which can be attributed to the absorptions expected for the -N̈-C=N- moiety and the C=C-C=N conjugated system respectively. The infrared spectrum shows the presence of a NH (3220 cm^{-1}),

cyano (2180 cm^{-1}), olefinic bond (1645 cm^{-1}) and an imine (1575 cm^{-1}). The nmr spectrum (δ) exhibited a 3 H triplet (J = 7 Hz) at 0.9 due to the terminal methyl of the n-butyl group, a 6 H multiplet at 1.1 - 2.0 due to the three methylenes of the n-butyl group, a 2 H multiplet at 2.4 attributed to the C_5-H, a 1 H multiplet at 3.6 due to the C_6-H, a complex 1 H multiplet at 6.3 due to the C_3-H, a 1 H multiplet ($J_{3,4}$ = 9 Hz, $J_{4,5}$ = 4 Hz) at 6.65 due to the C_4-H and a broad 1 H absorption at 7.45 due to the NH which exchanges with deuterium oxide. The isomeric structures LXXVI and LXXVII were dismissed since C_4-H and C_5-H of LXXVI would be expected to absorb in the range of δ 5.3 to 5.9[53,75] (cf also C_4-H and C_5-H of LXXIII) while the C_2-H of LXXVII would be expected to absorb at a lower field than δ 2.4.



LXXVI

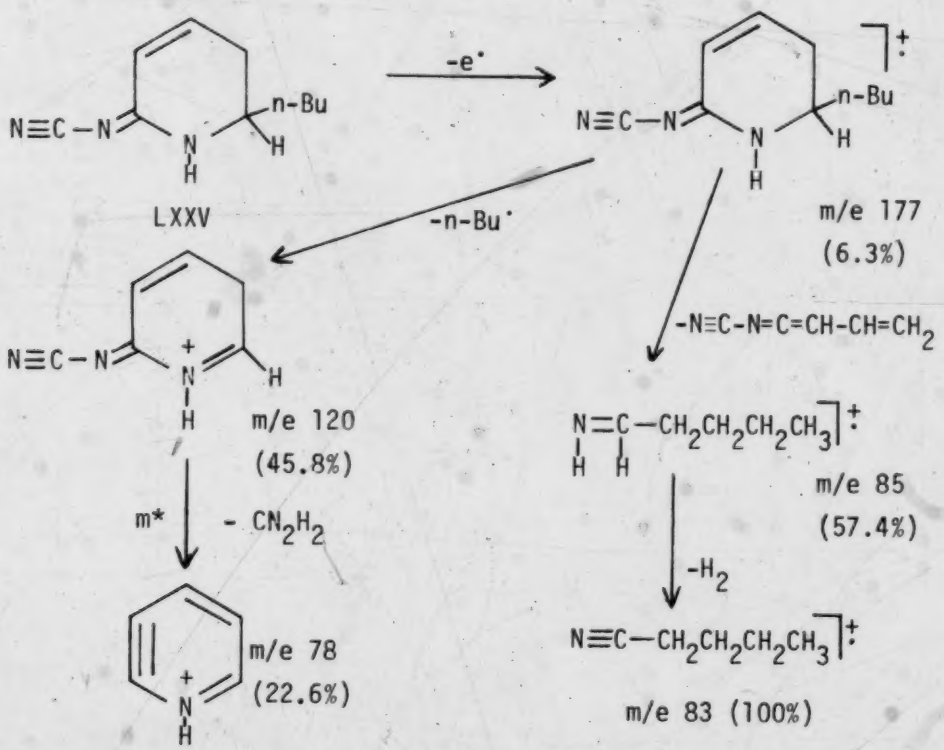


LXXVII

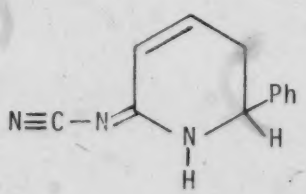
The mass spectrum of LXXV exhibited a molecular ion at m/e 177 (M^+ Calcd. for $C_{10}H_{15}N_3$: 177.1266; Found: 177.1265). The major fragmentation pathways as shown in Scheme 3 involve loss of the n-butyl group to produce a peak at m/e 120 ($C_6H_6N_3^+$) which in turn fragments to produce a peak at m/e 78 ($C_5H_4N^+$). The second fragmentation is confirmed by the presence of a metastable peak at m/e 50.7. The other fragmentation pathway involves a Retro Diels-Alder to produce a peak at m/e 85 ($C_5H_{11}N^+$). Subseqent loss of H_2 produces the base peak at m/e 83 ($C_5H_9N^+$).

Scheme 3

Major fragmentations of 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXV)



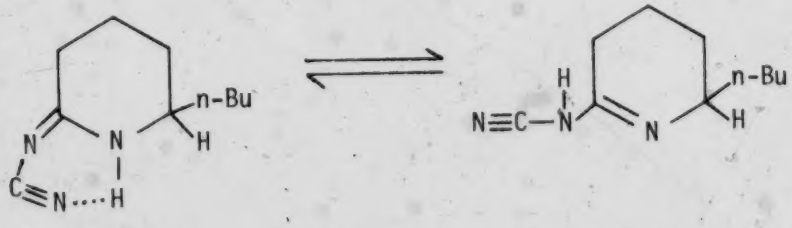
Stirring a suspension of neutral alumina (5 g) (Brockman Activity I) in 25 ml chloroform containing 3-phenyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (0.216 g) (LXXIII) for 72 hr afforded a product which exhibited spectral data consistent with 6-phenyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXVIII) in quantitative yield.



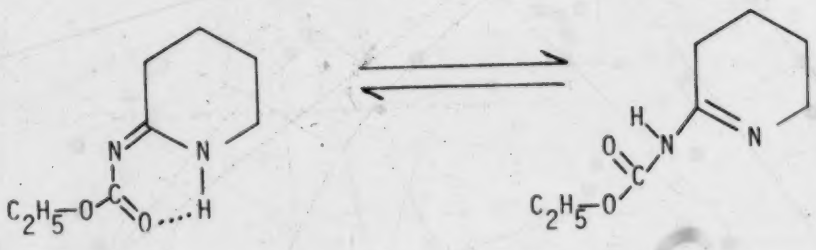
LXXVIII

Reduction of 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXV) with 10% palladium - charcoal and hydrogen gas at 35 psi yielded a tautomeric mixture of 6-n-butylpiperidylidene-2-cyanamide (LXXIXa) and 6-n-butyl-3,4,5,6-tetrahydropyridyl-2-cyanamide (LXXIXb) in quantitative yield.

The ultraviolet spectrum of this tautomeric mixture exhibited one band at 244 nm which can be attributed to the $\ddot{N}$-C=N group. The disappearance of the absorption at 288 nm attributed to the C=C-C=N conjugated system of LXXV provides further evidence in support of the structures assigned to LXXV and LXXIX. The infrared spectrum shows the presence of two NH bands. The piperidine NH of LXXIXa exhibits a band at 3240 cm^{-1} while the cyanamide of LXXIXb exhibits an NH band at 3120 cm^{-1}. The ir also displays a cyano band (2180 cm^{-1}) and two imine bands. The imine band of LXXIXa appears at 1605 cm^{-1} while LXXIXb exhibits an imine band at 1645 cm^{-1}. The shift of the imine band for LXXV at 1575 cm^{-1} to 1605 cm^{-1} for LXXIXa provides additional evidence for the presence of the C=C-C=N conjugated system present in LXXV. The existence of a similar tautomeric equilibrium between piperidylidene-2-ethoxycarbonylamide (LXXXa) and 3,4,5,6-tetrahydropyridyl-2-ethoxycarbonylamide (LXXXb) has been reported[60].



LXXIXa LXXIXb

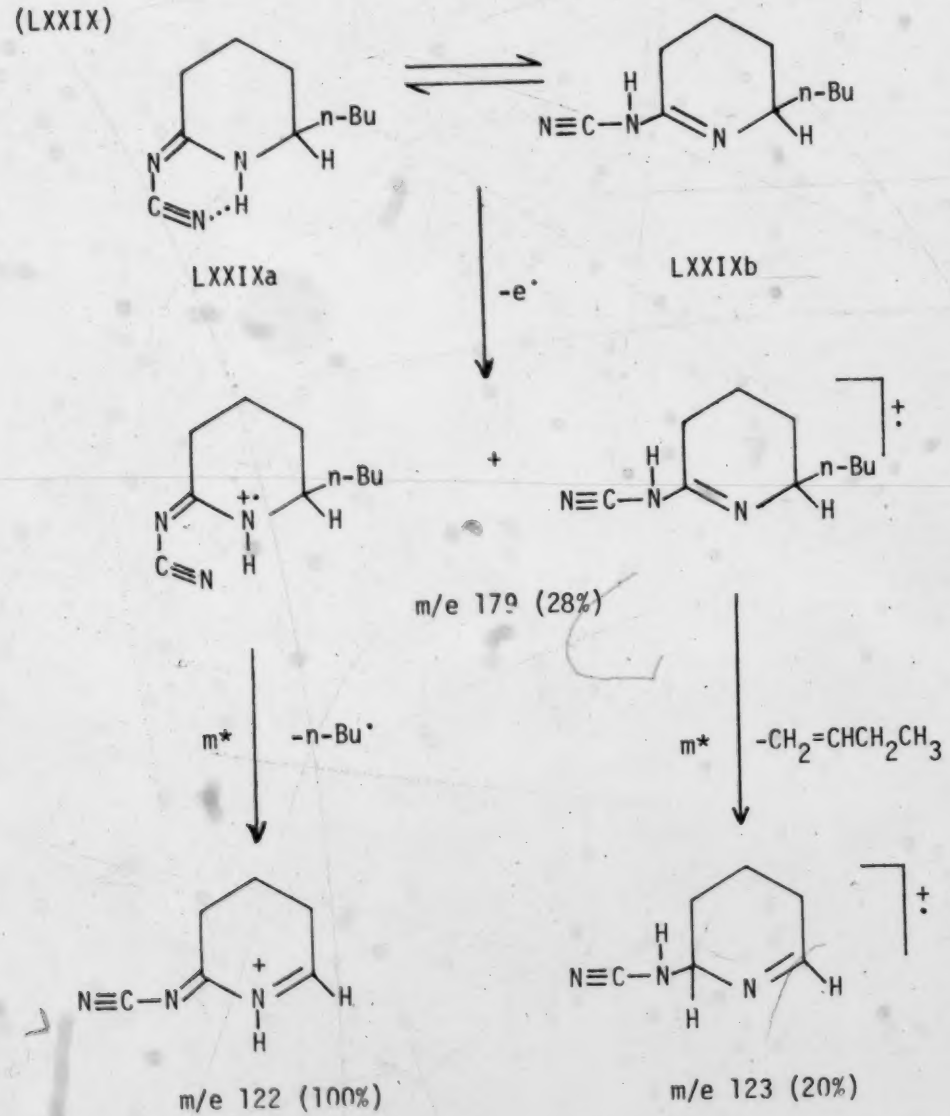


LXXXa LXXXb

The nmr spectrum (δ) of LXXIXa ⇌ LXXIXb exhibited a distorted 3 H triplet (J = 7 Hz) at 0.9 due to the terminal methyl of the n-butyl, a 10 H multiplet at 1.1 - 2.3 due to the three methylenes of the n-butyl, the C_4-H and C_5-H, a 2 H multiplet at 2.7 attributed to the C_3-H, a 1 H multiplet at 3.4 due to the C_6-H and a broad 1 H absorption at 8.0 due to the NH which exchanges with D_2O. It was not possible to detect separate signals for the tautomeric structures LXXIXa and LXXIXb. The mass spectrum of LXXIXa ⇌ LXXIXb exhibited a molecular ion at m/e 179 (M^+ Calcd. for $C_{10}H_{17}N_3$: 179.1422; Found; 179.1418). The molecular ion undergoes two major fragmentations. The loss of the n-butyl radical to give the base peak at m/e 122 ($C_6H_8N_3^+$) is supported by a metastable peak at m/e 83.1. The loss of n-butene by a McLafferty rearrangement to give a peak at m/e 123 is also supported by a metastable peak at m/e 84.5 (Scheme 4).

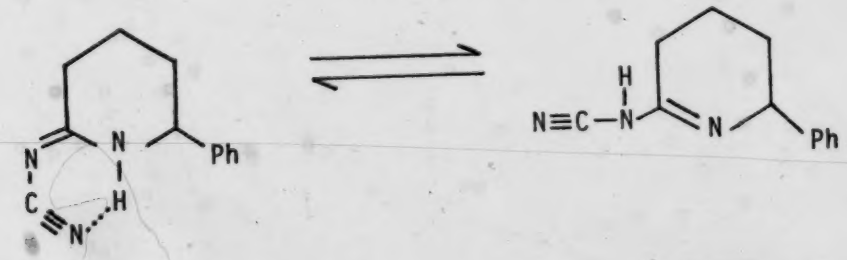
Scheme 4

Major fragmentation of the tautomeric mixture of 6-n-butylpiperidylidene-2-cyanamide and 6-n-butyl-1,2,3,4-tetrahydropyridyl-2-cyanamide (LXXIX)



Reduction of 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII) using 10% palladium - charcoal and hydrogen gas also afforded the tautomeric mixture LXXIXa ⇌ LXXIXb in quantitative yield.

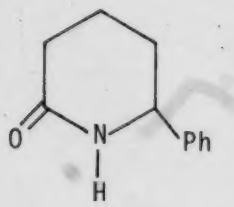
Similarly, reduction of 3-phenyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIV) and 6-phenyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXVIII) afforded a tautomeric mixture of 6-phenylpiperidylidene-2-cyanamide (LXXXIa) and 6-phenyl-3,4,5,6-tetrahydropyridyl-2-cyanamide (LXXXIb) in quantitative yield.



LXXXIa LXXXIb

Hydrolysis of the tautomeric mixture of 6-phenylpiperidylidene-2-cyanamide (LXXXIa) and 6-phenyl-3,4,5,6-tetrahydropyridyl-2-cyanamide (LXXXIb) using a 10% H_2SO_4 in methanol solution (1:10 v/v) gave rise to 6-phenyl-2-piperidone (LXXXII) (39%) thereby providing further evidence in support of structures LXXVIII and LXXXI. The infrared spectrum showed the presence of NH at 3180 cm^{-1} and a carbonyl at 1640 cm^{-1}. The appearance of the carbonyl band of 2-piperidone at 1635 cm^{-1} and N-ethyl-3-piperidone hydrochloride at 1724 cm^{-1} [74] indicates that LXXXII is 6-phenyl-2-piperidone rather than the isomeric 6-phenyl-3-piperidone. The nmr spectrum (δ) exhibited a 4 H multiplet at 1.5 - 2.1 due to the

C_4-H and C_5-H, a 2 H multiplet at 2.27 due to the C_3-H, a 1 H multiplet at 4.4 due to the C_6-H, a broad 1 H signal at 6.8 attributed to the NH which exchanges with deuterium oxide and a 5 H multiplet at 7.21 due to the phenyl hydrogens. The mass spectrum of LXXXII exhibited a molecular ion at m/e 175 (M^+ Calcd. for $C_{11}H_{13}NO$: 175.0997; Found: 175.1001.



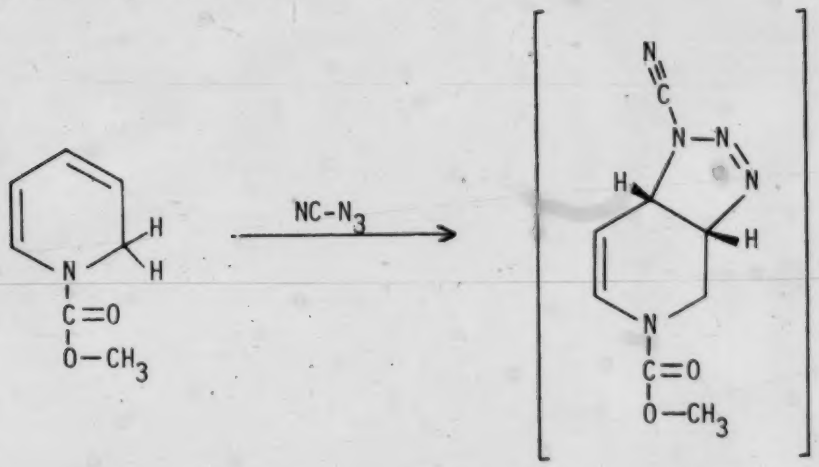
LXXXII

3.3.2.2.0 Reactions of cyanogen azide with N-substituted-1,2-dihydropyridines

In contrast to the reaction of cyanogen azide with 1,2-dihydropyridines where the substituent on the nitrogen atom was hydrogen, a series of reactions involving N-substituted-1,2-dihydropyridines with cyanogen azide were investigated. The formation of compounds where the N-cyano group of the imine function gave rise to two detectable stereoisomers increased the complexity of the nomenclature. To maintain consistency, the compounds designated syn refer to those in which the cyano group is cis to the C_3-H and the anti compounds those in which the cyano group is cis to the C_5-H.

The reaction of N-methoxycarbonyl-1,2-dihydropyridine with cyanogen azide afforded a 1:1 mixture of syn-N-methoxycarbonyl-1,2,3,4-tetra-

hydropyridylidene-4-cyanamide (LXXXIIIa) and anti-N-methoxycarbonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXIIIb) (20.8%). The mechanism proposed for this reaction involves a 1,3-dipolar cycloaddition of molecular cyanogen azide to N-methoxycarbonyl-1,2-dihydropyridine. The unstable triazoline intermediate produced eliminates nitrogen readily to form the pyridylidene-4-cyanamides LXXXIIIa and LXXXIIIb (see equation 10).

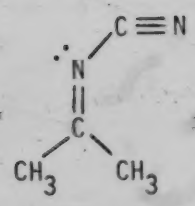


(10)

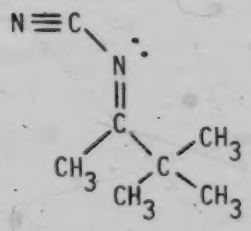
LXXXIIIa LXXXIIIb

The isolation of LXXXIII indicates that an electron withdrawing substituent on the nitrogen of the 1,2-dihydropyridine inhibits attack at the C_5-C_6 olefinic bond by steric hinderance and/or electronic deactivation. As a result, addition of cyanogen azide occurred exclusively at the C_3-C_4 olefinic bond. If the intermediate triazoline adduct formed is the product of electronic control, the nitrogen atom bearing the cyano group should be directed to the C-4 position of the ring. Unlike the product arising from addition of cyanogen azide to the C_5-C_6 olefinic bond of LVI to afford the bicyclic aziridine LXXIII, the facile loss of nitrogen in this reaction is accompanied by C_4-hydrogen migration and formation of the imine LXXXIII.

The reaction of cyanogen azide with simple alicyclic olefins has been reported to yield a mixture of syn and anti alkylidene cyanamides[68]. Nmr studies of these compounds indicated that the syn/anti ratios are dependent on the bulk of the substituents attached to the imine carbon. The chemical shift of the methyl groups of 1-methylethylidenecyanamide (LXXXIV) differ by 0.13 ppm with the methyl assigned syn to the cyano group exhibiting the resonance at lower field. The presence of a bulky group such as the t-butyl of 1-methyl-2,2-dimethylpropylidenecyanamide (LXXXV) gives rise to only one isomer. At elevated temperatures, the methyl resonances of the 1-methylethylidene-cyanamide isomers (LXXXIV) broaden and begin to coalesce. A temperature study[77] of LXXXIV showed the coalescence temperature for the methyl resonances to be 85°C.



LXXXIV



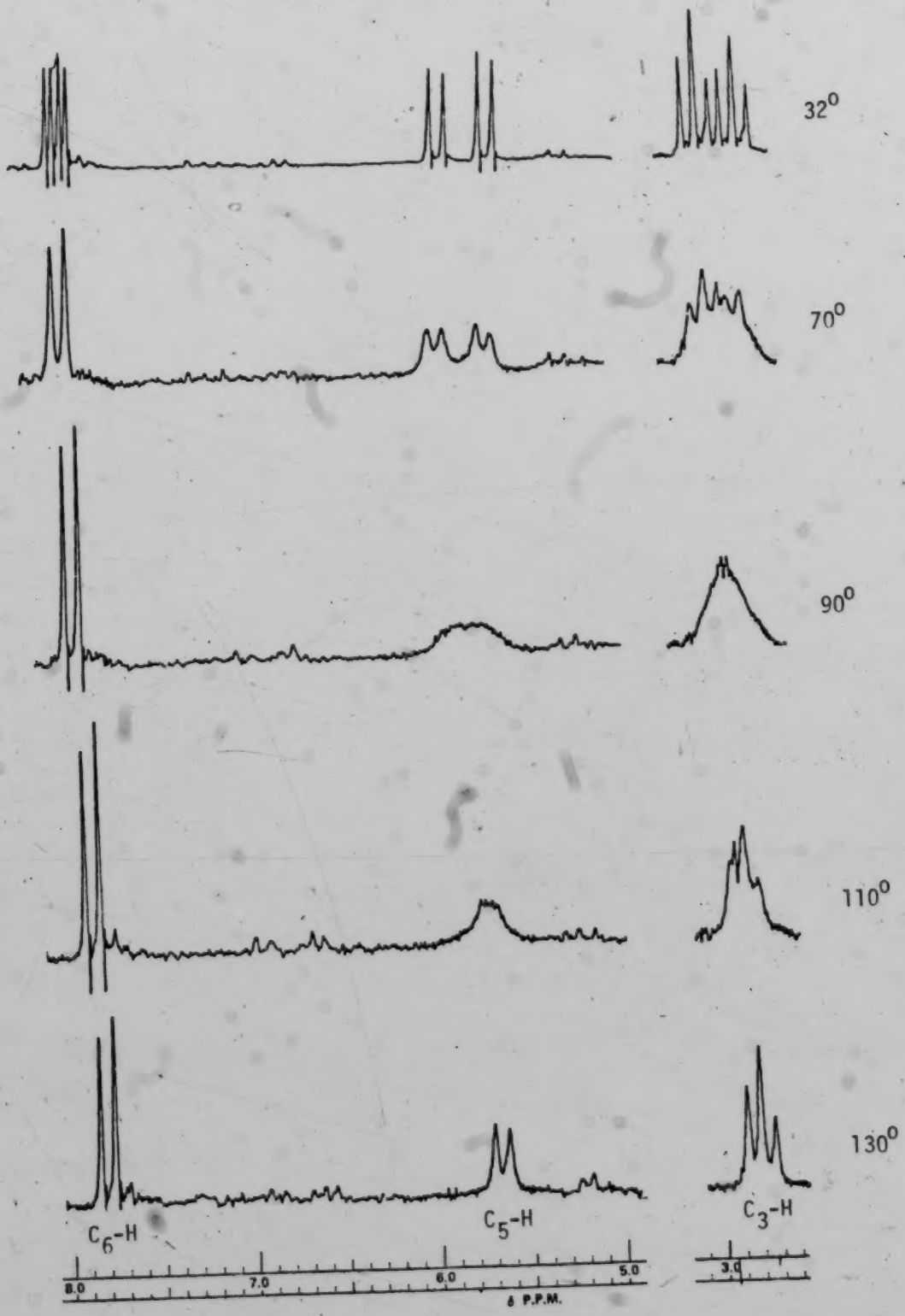
LXXXV

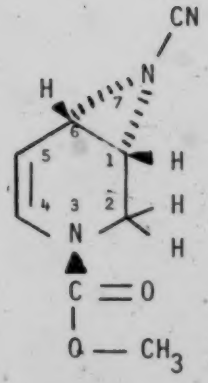
The formation of LXXXIIIa and b indicates the similarity in reactivity of the C_3-C_4 olefinic bond of N-methoxycarbonyl-1,2-dihydropyridine and the olefinic bond of simple alkenes. The absence of steric effects at the C_3 and C_5 position in LXXXIII results in a syn/anti ratio of 1:1. A temperature study effected on a stereoisomeric mixture of LXXXIIIa and b in DMSO-d_6 indicated the coalescense temperature to be approximately 90° which is similar to that reported for LXXXIV[77]. Further heating to 140° caused some decomposition . The ratio of syn/anti isomers returned to 1:1 after cooling to 25° (see Figure 1).

The products from the reaction of N-methoxycarbonyl-1,2-dihydropyridine and cyanogen azide were assigned structures LXXXIIIa and b rather than LXXXVIa and b on the basis of the uv, ir and nmr spectral data. The ultra violet spectrum of LXXXVI would be expected to show one absorption band at 230 nm for the N-C=C system[78]. The C_4-C_5 olefinic band in the infrared spectrum of LXXXVI would be expected to appear at a wave number higher than 1590 cm^{-1}. The absence of $J_{5,6}$ coupling constant in the nmr spectrum precludes structures LXXXVI a and b.

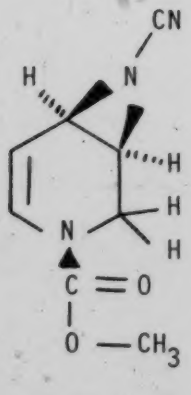
Figure 1

NMR temperature study of N-methoxycarbonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXIII)





LXXXVIa



LXXXVIb

It is also unlikely that the N_3-methoxycarbonyl group of LXXXVI would exist as one nitrogen invertomer in solution since nitrogen inversion in a six membered ring would be expected to be very rapid on the nmr time scale. Nitrogen inversion of N-cyanoaziridines is reported to be very rapid[68].

The uv, ir, nmr and mass spectra are therefore consistent with the assigned structures LXXXIIIa and b. The ultraviolet spectrum in absolute ethanol exhibits one band at 333 nm. This corresponds well with the λ max expected for the N-C=C-C=N system. The infrared spectrum indicated the presence of a cyano (2180 cm^{-1}), a carbonyl (1730 cm^{-1}), an imine (1590 cm^{-1}) and an olefinic bond (1560 cm^{-1}).

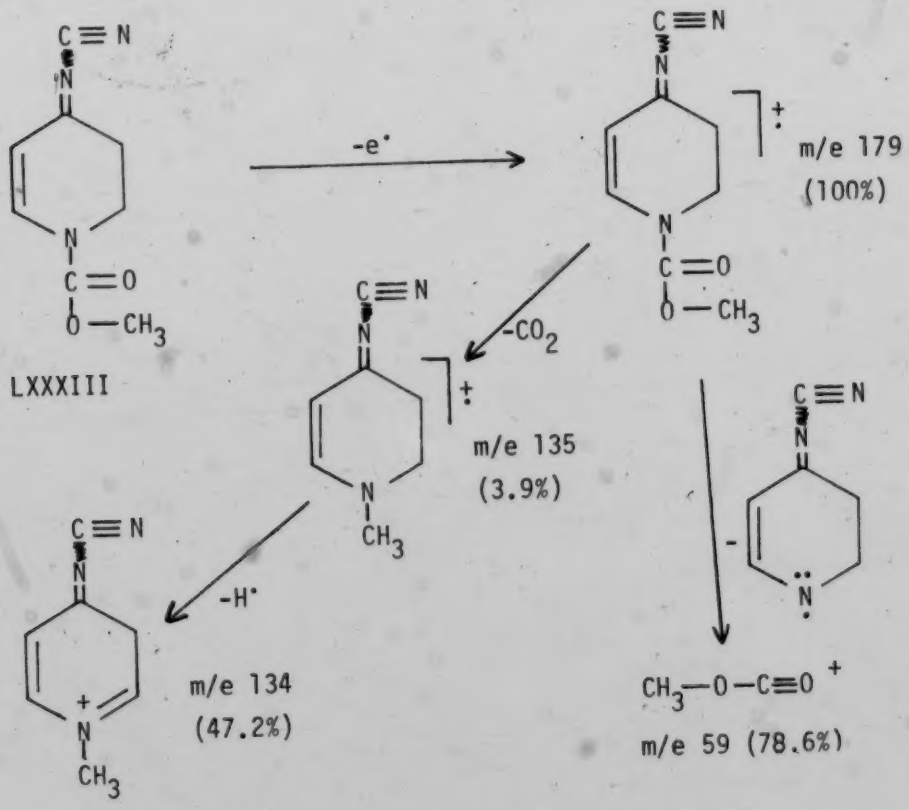
The nmr spectrum (δ) of LXXXIIIa and b exhibited a 2 H triplet ($J_{2,3}$ = 7.5 Hz) at 2.74 (LXXXIIIb) and 2.95 (LXXXIIIa) attributed to the C_3-H which collapsed to two single peaks upon irradiation of the C_2-H at 3.9. The two triplets due to the C_3-H also coalesce to one triplet ($J_{2,3}$ = 7.5 Hz) at 2.82 upon heating to 130°C. The nmr spectrum

also exhibited a 3 H singlet at 3.81 due to the methoxy methyl, a 2 H triplet ($J_{2,3}$ = 7.5 Hz) at 3.90 due to C_2-H and a 1 H doublet ($J_{5,6}$ = 8 Hz) at 5.59 (LXXXIIIa) and 5.85 (LXXXIIIb) due to C_5-H which collapsed to two single peaks upon irradiation of the C_6-H at 7.93. The two doublets at 5.59 and 5.85 coalesce to one doublet ($J_{5,6}$ = 8 Hz) at 5.68 upon heating to 130°. The spectrum also exhibited a 1 H doublet ($J_{5,6}$ = 8 Hz) at 7.90 (LXXXIIIb) and 7.95 (LXXXIIIa) due to C_6-H which selectively collapse to singlets upon irradiation of the absorption at 5.85 due to C_5-H of LXXXIIIb and the absorption at 5.59 due to C_5-H of LXXXIIIa respectively thereby providing further evidence for the presence of two isomers.

The mass spectrum of LXXXIIIa and LXXXIIIb exhibited a molecular ion at m/e 179 (M^+ Calcd. for $C_8H_9N_3O_2$: 179.0694; Found: 179.0694. The molecular ion which is the base peak fragments by two major pathways (Scheme 5). Expulsion of carbon dioxide followed by loss of a hydrogen radical gives rise to a peak at m/e 134 ($C_7H_3N_3^+$). Fragmentation of the carbamate function also produces a peak at m/e 59 ($C_2H_3O_2^+$).

Scheme 5

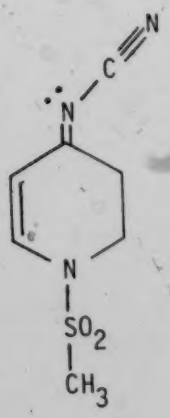
Major fragmentations of the 1:1 isomeric mixture of syn-N-methoxy-carbonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide and anti-N- methoxy-carbonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXIII)



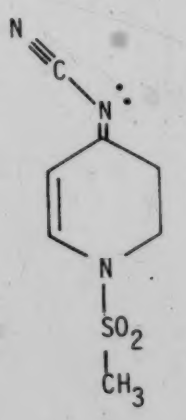
The reaction of N-methanesulfonyl-1,2-dihydropyridine with cyanogen azide afforded a 1:1 mixture of syn-N-methanesulfonyl-1,2,3,4-tetra-hydropyridylidene-4-cyanamide (LXXXVIIa) and anti-N-methanesulfonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXVIIb) (14.5%). The structures assigned to this isomeric mixture is consistent with its infrared, nmr and mass spectra. Unreacted N-methanesulfonyl-1,2-dihydro-

pyridine (40.1%) was also recovered.

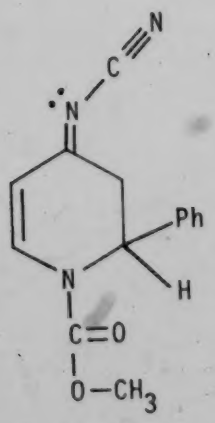
The reaction of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine with cyanogen azide gave rise to a 1:1 mixture of syn-N-methoxycarbonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXVIIIa) and anti-N-methoxycarbonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXVIIIb) (14.6%) which was in agreement with its ir, nmr and mass spectra. Unreacted N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (66.3%) was recovered.



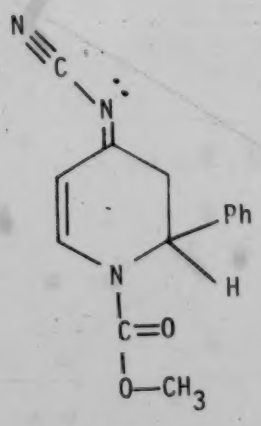
LXXXVIIa



LXXXVIIb

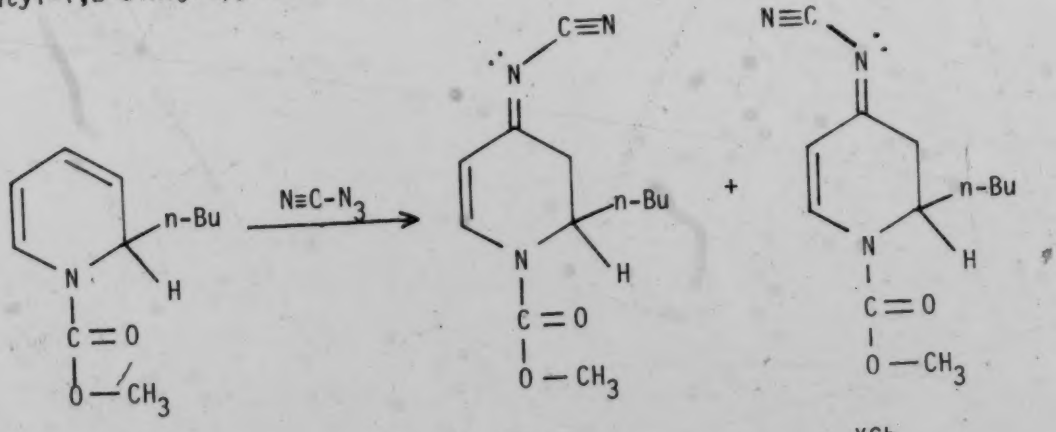


LXXXVIIIa



LXXXVIIIb

Similarly, the reaction of N-methoxycarbonyl-2-n-butyl-1,2-dihydropyridine (LXXXIX) with cyanogen azide afforded a 1:1 mixture of syn-N-methoxycarbonyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCa) and anti-N-methoxycarbonyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCb) (41.6%). N-methoxycarbonyl-2-n-butyl-1,2-dihdyropyridine (LXXXIX) (21.7%) was recovered.



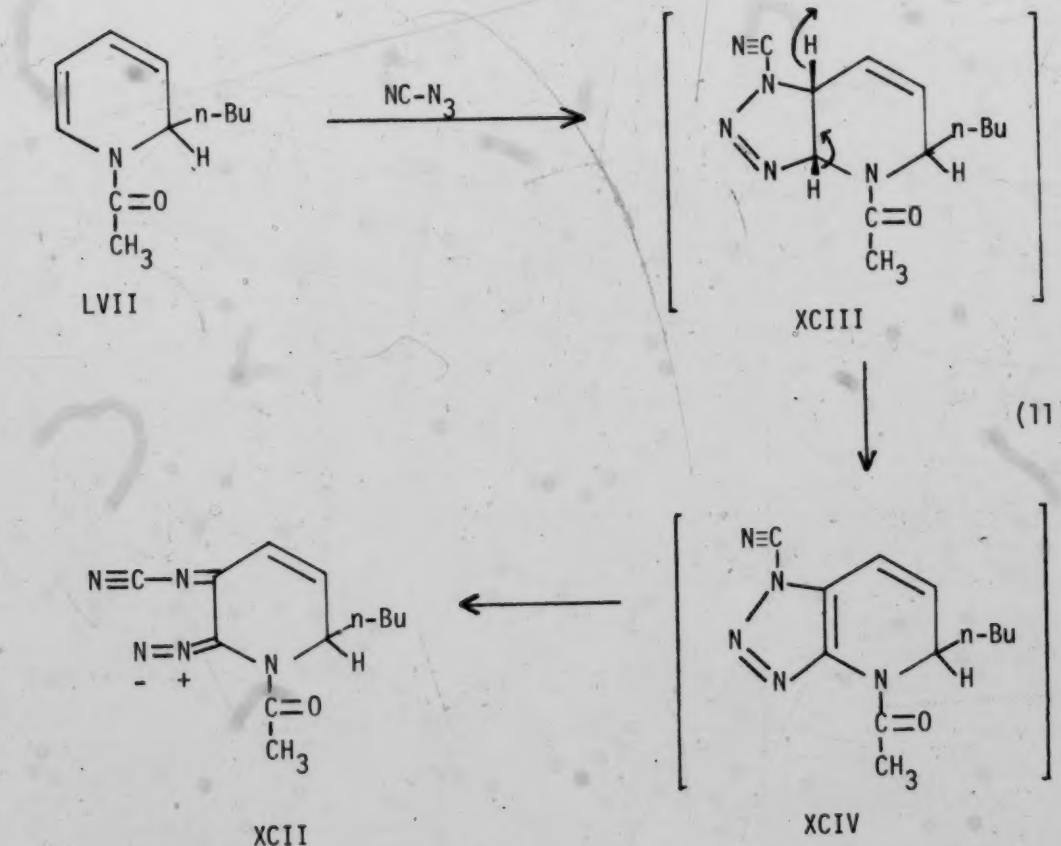
LXXXIX XCa XCb

The ultraviolet spectrum of XC in absolute ethanol displayed a λ max at 338 nm. The infrared spectrum showed the presence of a cyano (2180 cm^{-1}), a carbonyl (1730 cm^{-1}), an imine (1580 cm^{-1}) and an olefinic bond (1560 cm^{-1}). The mass spectrum exhibited a molecular ion at m/e 235 (Calcd. for $C_{12}H_{17}N_3O_2$: 235.1321; Found: 235.1317).

The coupling observed in the 60 MHz nmr spectrum (δ) of XCa and XCb differed from that of the previous mixtures of isomers. The C_6-H appeared as a doublet ($J_{5,6}$ = 8.0 Hz) of doublets ($J_{2,6}$ = 1 Hz) at 7.72 (XCb) and 7.73 (XCa). The C_5-H gave rise to a doublet ($J_{3,5}$ = 1.25 Hz) of doublets ($J_{5,6}$ = 8 Hz) at 5.68 (XCa) and 5.97 (XCb).

$J_{2,6}$ coupling was not observed in the spectra of the isomeric mixtures discussed previously.

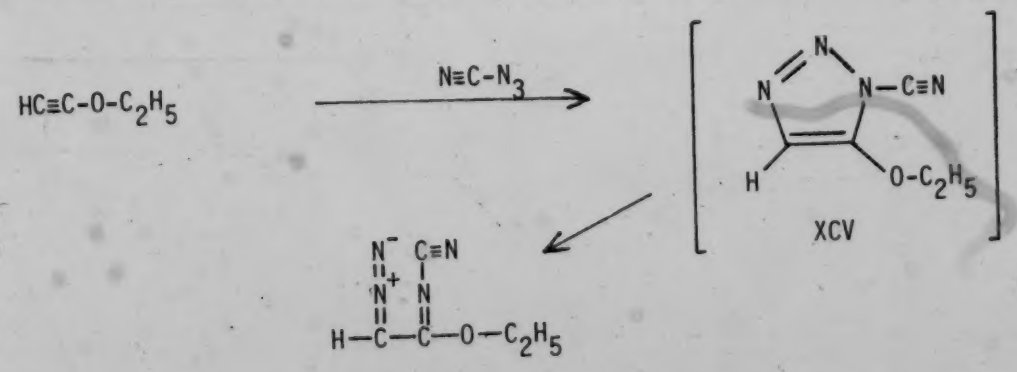
The reaction of N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) with cyanogen azide yielded a 1:1 stereoisomeric mixture of syn-N-acetyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCIa) and anti-N-acetyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCIb) (7.2%), N-acetyl-6-n-butyl-2-diazo-1,2,3,6-tetrahydropyridylidene-3-cyanamide (XCII) (3.9%), 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII) (25.3%) as well as unreacted N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) (44.7%). The isolation of both XCIa and b in addition to LXXIII and XCII indicates that a 1,3-dipolar cycloaddition reaction occurred at both the C_3-C_4 and C_5-C_6 olefinic bonds. The 1:1 mixture of XCIa and XCIb probably arises via the mechanism in equation 10. On the other hand, addition of cyanogen azide to the C_5-C_6 olefinic bond of LVII would give rise to the intermediate triazoline XCIII. If the triazoline adduct XCIII is a product of electronic control and the enamine 5,6-olefinic bond is deactivated by the acetyl group, the nitrogen bearing the cyano group should be directed to the C_5 position. The absence of products resulting from addition of cyanogen azide to the C_5-C_6 bond of N-methoxycarbonyl-1,2-dihydropyridine and N-methanesulfonyl-1,2-dihydropyridine may be due to a greater steric effect exhibited by the N-methanesulfonyl and N-methoxycarbonyl substituents. Elimination of a molecule of hydrogen from XCIII would give the more aromatic XCIV. Ring opening of the bicyclic adduct XCIV would then give rise to XCII (see equation 11).



LVII XCIII (11)

XCII XCIV

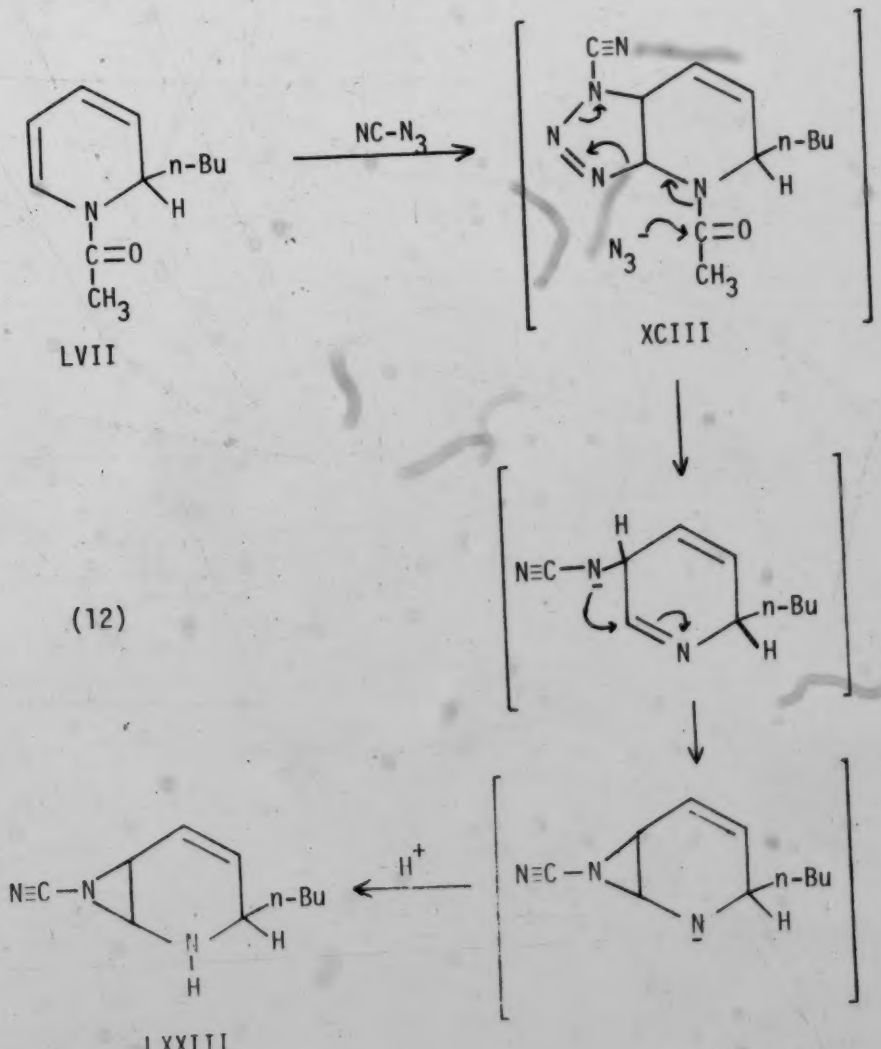
The proposed ring opening of the triazole adduct XCIV is similar to that reported for the adduct XCV obtained from reaction of ethoxyacetylene and cyanogen azide[79]. A ring opening has also been postulated for the adduct of ethoxyacetylene and p-toluenesulfonyl azide[80].



XCV

XCVI

One plausible mechanism which would explain the formation of LXXIII involves nucleophilic attack of the intermediate triazoline XCIII at the amide carbonyl by azide anion. Subsequent ring opening, loss of nitrogen and ring closure to a bicyclic aziridine would yield LXXIII on work up (see equation 12).



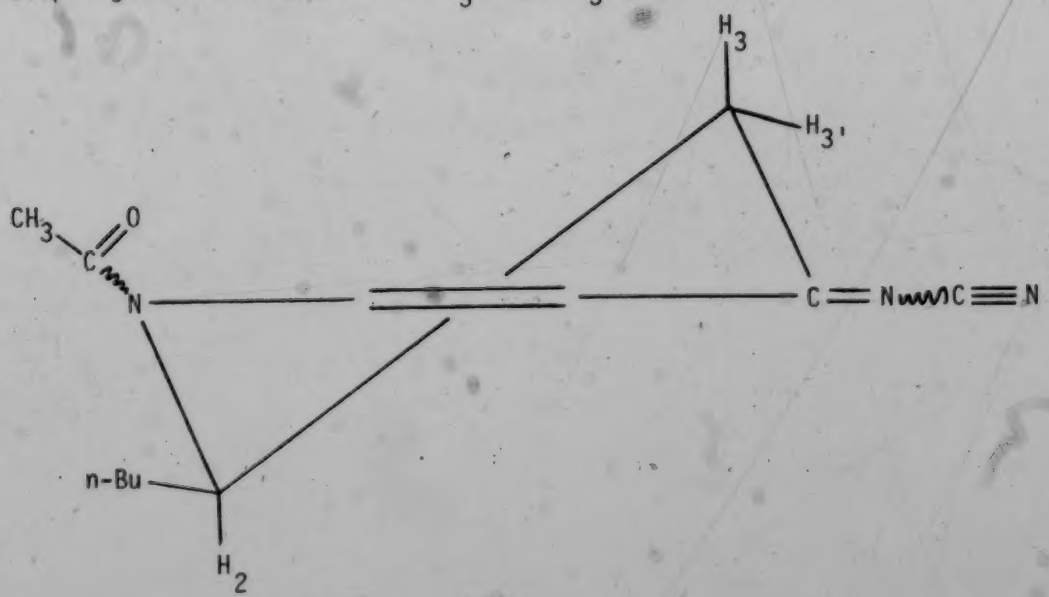
LVII

XCIII

(12)

LXXIII

The structures assigned to syn-N-acetyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCIa) and anti-N-acetyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCIb) are consistent with their infrared, nmr and mass spectra. A 220 MHz spectrum (δ) of the 1:1 isomeric mixture exhibited a 3 H distorted triplet (J = 7 Hz) at 0.9 due to the methyl of the n-butyl group, a 6 H multiplet at 1.1 - 1.8 due to the three methylenes of the n-butyl group and a 3 H singlet at 2.4 attributed to the acetyl group. Two doublets ($J_{3,3'}$ = 16 Hz) due to C_3-H' appeared at 2.58 (XCIb) and 3.16 (XCIa). Two doublets ($J_{2,3}$ = 7.5 Hz) of doublets ($J_{3,3'}$ = 16 Hz) due to C_3-H appeared at 2.70 (XCIb) and 2.81 (XCIa). One possible representation for this ring system is structure XCIc. The spectral data indicates that the C_3'-H and the n-butyl group are both equatorial. The C_2-H and C_3-H are both axial. Axial-equatorial coupling $J_{2,3'}$ was not observed in the spectrum although axial-axial coupling $J_{2,3}$ was 7.5 Hz. Geminal coupling of the nonequivalent C_3'-H and C_3-H was 16 Hz.



XCIc

The spectra exhibited by 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII) was identical to the infrared and nmr spectra of the same product obtained from reaction of cyanogen azide and 2-n-butyl-1,2-dihydropyridine (LVI) described previously.

The structure of N-acetyl-6-n-butyl-2-diazo-1,2,3,6-tetrahydropyridylidene-3-cyanamide (XCII) was assigned on the basis of its ir, nmr and mass spectra as well as comparison to the ir data reported for α-diazo-N-cyanoacetimidate (XCVI)[79]. The infrared spectrum of XCII showed the presence of a cyano (2180 cm^{-1}), a diazo (2090 cm^{-1}), a carbonyl (1700 cm^{-1}), an imine (1555 cm^{-1}) and an olefinic bond (1545 cm^{-1}). The ir spectrum of α-diazo-N-cyanoacetimidate (XCVI) is reported to have bands at 2200 cm^{-1} (C≡N), 2120 cm^{-1} (=N_2) and 1575 cm^{-1} (C=N)[79]. The nmr spectrum (δ) of XCII exhibited a distorted 3 H multiplet (J = 7 Hz) at 0.9 due to the terminal methyl of the n-butyl group, a 6 H multiplet at 1.1 - 1.9 due to the three methylenes of the n-butyl group, a 3 H singlet at 2.5 attributed to the acetyl methyl, a 1 H multiplet at 5.11 due to the C_6-H and a complex 2 H multiplet at 5.7 - 6.25 attributed to the C_4-H and C_5-H. The mass spectrum exhibited a molecular ion at m/e 245 (Calcd. for $C_{12}H_{15}N_5O$: 245.1276; Found: 245.1271). The first fragment appeared at m/e 217 (Calcd. for $C_{12}H_{15}N_3O$: 217.1215; Found: 217.1218) which corresponds to the expected loss of nitrogen from the molecular ion.

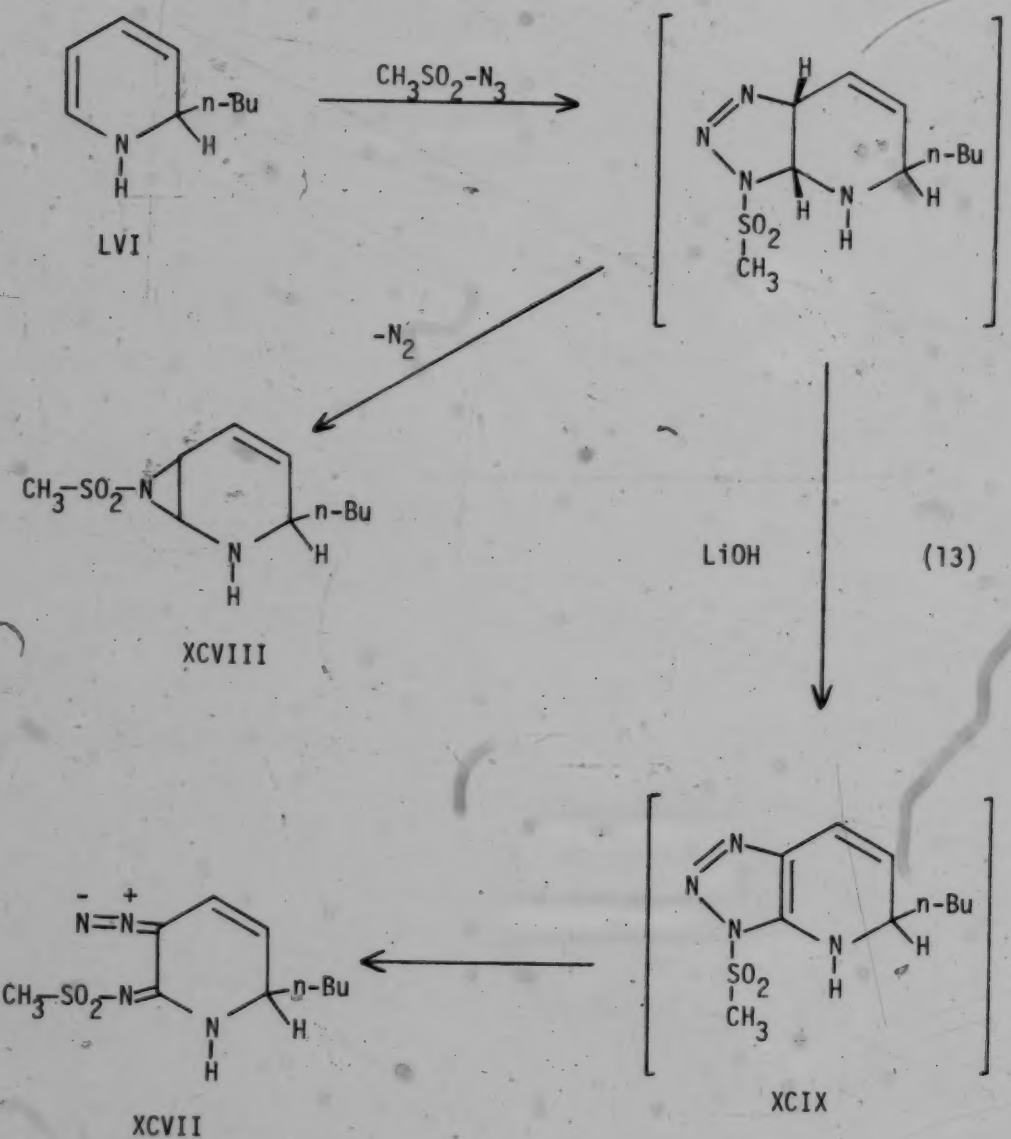
3.3.2.3.0 Reactions of 1,2-dihydropyridines with sulfonyl azides, carbonyl azides and hydrazoic acid

The reaction of 2-n-butyl-1,2-dihydropyridine (LVI) with a series of sulfonyl azides, carbonyl azides and hydrazoic acid was also investigated to determine the generality of the 1,3-dipolar cycloaddition reaction and to prepare novel nitrogen heterocycles with potential pharmacological activity. The preparation of LVI by hydrolysis of N-lithio-2-n-butyl-1,2-dihydropyridines (XXX) with an excess of water followed by treatment with anhydrous sodium sulfate yielded lithium hydroxide free solutions. The preparation of LVI from XXX with one equivalent of water yielded solutions containing 5% lithium hydroxide. In the reactions of LVI with sulfonyl azides, both methods of preparation were employed. The remaining reactions to be discussed employed the use of only lithium hydroxide free solutions.

The reaction of 2-n-butyl-1,2-dihydropyridine (LVI) with one equivalent of methane sulfonyl azide in the presence of lithium hydroxide (5%) afforded 6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridyl-idene-2-methanesulfonamide (XCVII) (17.5%) and 3-n-butyl-7-methane-sulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (XCVIII) (42.9%).

The proposed mechanism responsible for the formation of XCVII is likely similar to that proposed for the reaction of 2-n-butyl-1,2-dihydropyridine (LVI) with cyanogen azide (see equation 8). Lithium hydroxide which is present in the reaction mixture could abstract a proton from one of the bridgehead positions of the intermediate triazoline. Elimination of hydride would then afford the triazole

intermediate (XCIX) which readily opens to yield XCVII as shown in equation 13. This ring opening employs the same mechanism proposed for the formation of XCII as well as the reported cyanogen azide[79] and p-toluenesulfonyl azide[80] adducts formed with ethoxyacetylene.

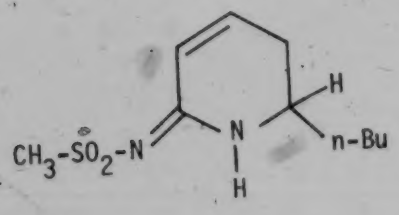


The structure assigned to 6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridylidene-2-methanesulfonamide (XCVII) is in agreement with its infrared, nmr and mass spectra. The infrared spectrum shows the presence of a secondary amine (3290 cm^{-1}), a diazo group (2090 cm^{-1}), an olefinic bond (1640 cm^{-1}) and an imine (1580 cm^{-1}). The nmr spectrum (δ) exhibits a 3 H distorted triplet (J = 7 Hz) at 0.96 due to the terminal methyl of the n-butyl group, a 6 H multiplet at 1.15 - 1.85 due to the three methylenes of the n-butyl group, a 3 H singlet at 3.02 due to the methanesulfonate, a 1 H multiplet at 4.33 attributed to the C_6-H, a 1 H doublet ($J_{1,5}$ = 1.5 Hz) of doublets ($J_{5,6}$ = 4 Hz) of doublets ($J_{4,5}$ = 10 Hz) which collapses to a doublet ($J_{5,6}$ = 4 Hz) of doublets ($J_{4,5}$ = 10 Hz) upon deuterium oxide exchange of the NH at 5.3 due to the C_5-H, a 1 H doublet ($J_{4,6}$ = 1.5 Hz) of doublets ($J_{4,5}$ = 10 Hz) at 6.1 due to the C_4-H and a 1 H broad signal at 8.1 due to the NH which exchanges with deuterium oxide. The mass spectrum exhibited a molecular ion at m/e 256 (Calcd. for $C_{10}H_{16}N_4O_2{}^{32}S$: 256.0994; Found: 256.0984). A fragment at m/e 228 (Calcd. for $C_{10}H_{16}N_2O_2{}^{32}S$: 228.0933; Found: 228.0934) formed by loss of nitrogen also verified the structure. The structure assigned to XCVIII is consistent with its ir, nmr and mass spectra. Compound XCVIII exhibited spectral data similar to that of LXXIII described previously.

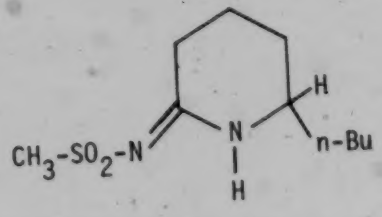
The reaction of a lithium hydroxide free solution of 2-n-butyl-1,2-dihydropyridine with methane sulfonyl azide afforded 3-n-butyl-7-methanesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (XCVIII) in quantitative yield.

Elution of XCVIII from a neutral alumina (Brockman Activity I) column afforded 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-methanesulfonamide (C) in quantitative yields. Compound C exhibited infrared, nmr and mass spectra data consistent with the assigned structure.

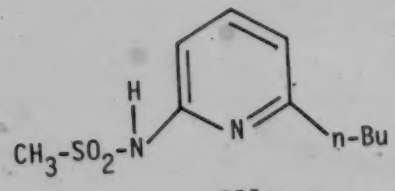
Reduction of XCVIII and C with 10% palladium - charcoal and hydrogen gas at 35 psi afforded 6-n-butylpiperidylidene-2-methanesulfonamide (CI) (91.8% and 91.5% respectively) and 6-n-butylpyridyl-2-methanesulfonamide (CII) (7.5% and 7.8% respectively). 6-n-Butylpyridyl-2-methanesulfonamide (CII) likely arises as a result of dehydrogenation of C^{60}. The infrared, nmr and mass spectra of 6-n-butylpiperidylidene-2-methanesulfonamide (CI) did not display any evidence which would suggest the presence of a second tautomer.



C



CI



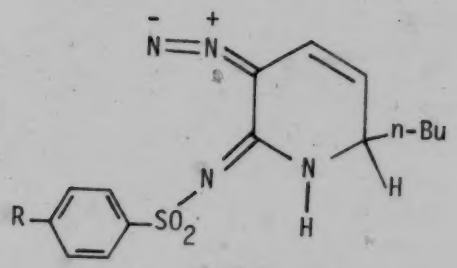
CII

The reaction of 2-n-butyl-1,2-dihydropyridine (LVI) with benzene sulfonyl azide in the presence of lithium hydroxide (5%) afforded 6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridylidene-2-benzenesulfonamide

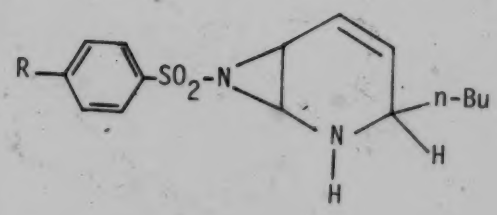
(CIII) (34.1%) and 3-n-butyl-7-benzenesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CIV) (40.7%). The same reaction in the absence of lithium hydroxide afforded CIV in quantitative yield.

The reaction of 2-n-butyl-1,2-dihydropyridine (LVI) with N-acetylsulfanilyl azide with lithium hydroxide (5%) present yielded 6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridylidene-2-N-acetylsulfanil amide (CV) (12.5%) and 3-n-butyl-7-N-acetylsulfanilyl-2,7-diaza-bicyclo [4.1.0] hept-4-ene (CVI) (79%). When the reaction was carried out in the absence of lithium hydroxide CVI was obtained in quantitative yield.

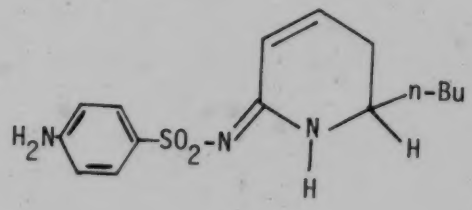
The reaction of 2-n-butyl-1,2-dihydropyridine (LVI) with sulfanil azide with 5% lithium hydroxide present afforded 6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridylidene-2-sulfanilamide (CVII) (1.3%) and 3-n-butyl-7-sulfanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CVIII) (78.5%). In the absence of lithium hydroxide CVIII was obtained in quantitative yield. Elution of CVIII from a neutral alumina (Brockman Activity I) column after standing for one week afforded 6-n-butyl-1,2,5,6-tetra-hydropyridylidene-2-sulfanilamide (CIX) (92%). Reduction of CVIII and CIX with 10% palladium - charcoal and hydrogen gas at 35 psi afforded quantitative yields of 6-n-butylpiperidylidene-2-sulfanil-amide (CX). The infrared, nmr and mass spectra of CX did not exhibit any evidence which would suggest the presence of a second tautomeric species.



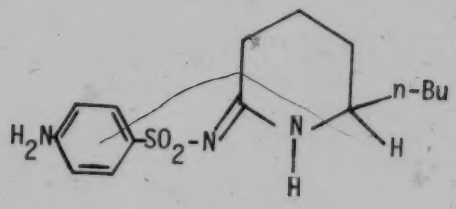
R = H (CIII), CH_3CONH (CV), H_2N (CVII)



R = H (CIV), CH_3CONH (CVI), H_2N (CVIII)



CIX

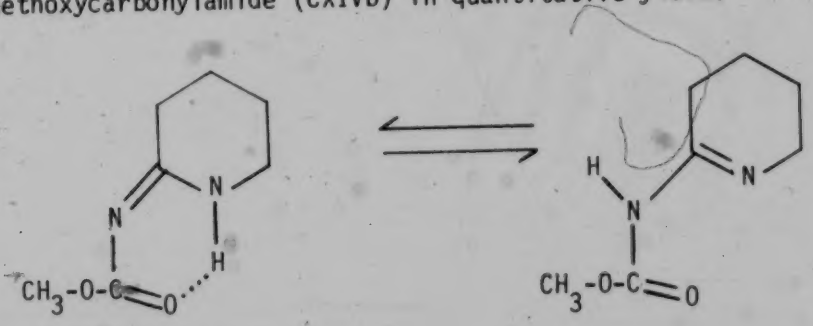


CX

The reaction of 2-n-butyl-1,2-dihydropyridine (LVI) with benzoyl azide afforded 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-phenylcarbonyl-amide (CXI) (20.1%). The nmr spectrum of the crude reaction mixture exhibited signals characteristic of 3-n-butyl-7-benzoyl-2,7-diazabicyclo [4.1.0] hept-4-ene, however only the ring opened product CXI was recovered after preparative tlc. The reaction of LVI with a five fold excess of benzoyl azide afforded CXI (39.7%).

Treatment of 2-n-butyl-1,2-dihydropyridine (LVI) with methoxy-carbonylazide gave 3-n-butyl-7-methoxycarbonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CXII) (100%). Preparative tlc of CXII on silica gel G plates afforded the ring opened product 6-n-butyl-1,2,5,6-tetrahydro-pyridylidene-2-methoxycarbonylamide (CXIII) in quantitative yield.

Reduction of CXII using 10% palladium - charcoal and hydrogen gas at 35 psi afforded a tautomeric mixture of 6-n-butylpiperidylidene-2-methoxycarbonylamide (CXIVa) and 6-n-butyl-3,4,5,6-tetrahydropyridyl-2-methoxycarbonylamide (CXIVb) in quantitative yield.

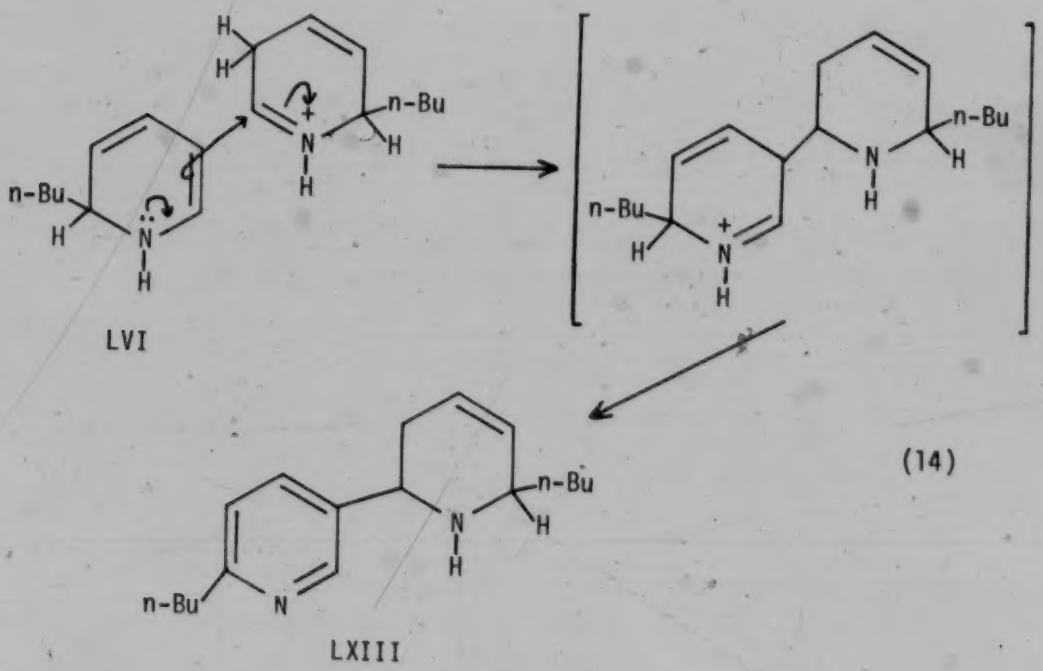


CXIVa CXIVb

The tautomeric mixture of CXIVa and b exhibited spectral data consistent with the assigned structures. For example, the infrared spectrum showed two NH stretching bands at 3210 cm^{-1} (CXIVa) and 3150 cm^{-1} (CXIVb). The presence of strong bands for the imine and carbonyl groups of both tautomers in the 1575 to 1650 cm^{-1} region prevented assignment of separate bands for the carbonyl and imino groups of CXIVa and CXIVb. The structures reported[60] for piperidylidene-2-ethoxycarbonylamide (LXXXa) and 3,4,5,6-tetrahydropyridyl-2-ethoxy-carbonylamide (LXXXb) and the structures of 6-n-butylpiperidylidene-2-cyanamide (LXXIXa) and 6-n-butyl-3,4,5,6-tetrahydropyridyl-2-cyanamide (LXXIXb) described previously provide further evidence in support of the tautomeric CXIVa and b.

The reaction of 2-n-butyl-1,2-dihydropyridine (LVI) with hydrazoic acid yielded the unexpected 6,6'-di-n-butyl-1,2,3,6-tetrahydro-2,3'-dipyridyl (LXIII) (64.7%) and 2-n-butylpyridine (LVIII) (12.2%).

The most likely mechanism for the formation of LXIII involves protonation of LVI at the C_5-position by hydrazoic acid to give a 2,5-dihydropyridyl iminium species which could then undergo nucleophilic attack at the highly electrophilic 6-position by LVI. Subsequent aromatization of the 2,5-dihydropyridine dimeric intermediate would afford LXIII (see equation 14).



LVI

LXIII

(14)

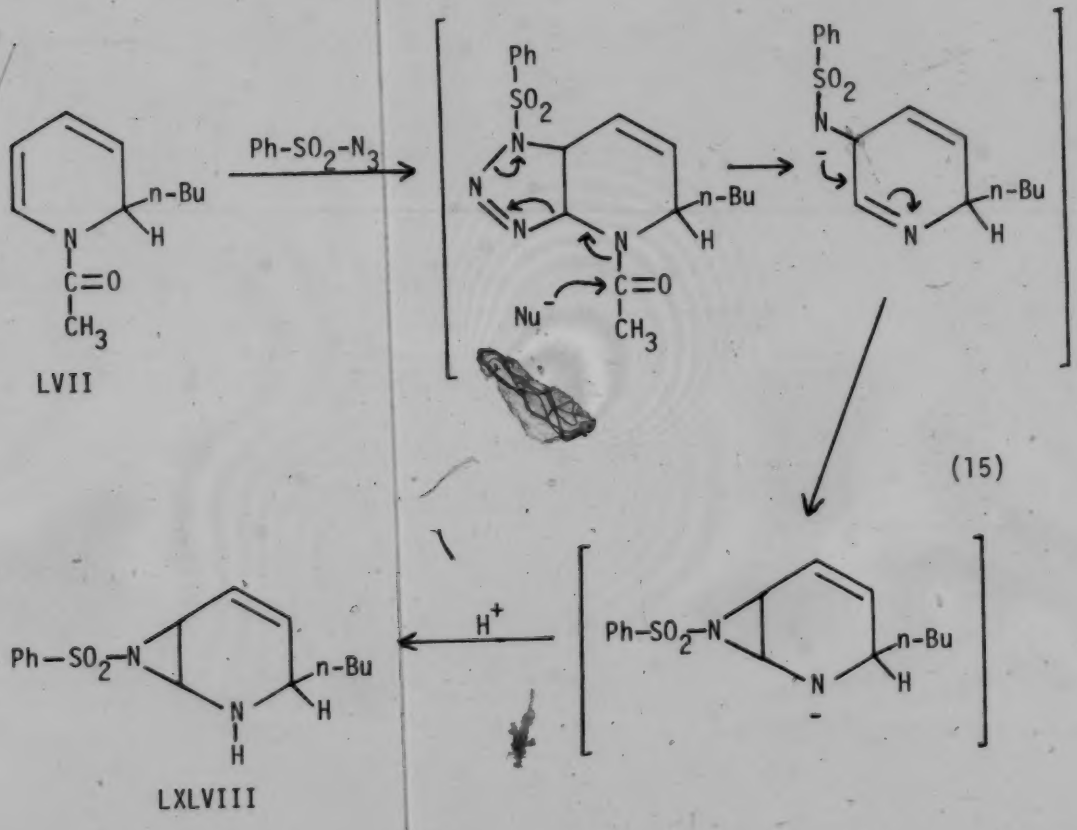
3.3.2.4.0 Reactions of N-substituted-1,2-dihydropyridines with benzenesulfonyl azide

The 1,3-dipolar cycloaddition reaction of N-substituted-1,2-dihydropyridines with benzenesulfonyl azide was also investigated. It was of interest to determine whether other organic azides would afford products similar to those obtained when cyanogen azide was

used as the dipole.

The reaction of N-methoxycarbonyl-1,2-dihydropyridine with benzenesulfonyl azide did not proceed and unreacted starting materials were recovered after 12 days at 25°.

Reaction of N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) with benzenesulfonyl azide for 3 days afforded unreacted benzenesulfonyl azide (46.4%), unreacted N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) (67%) and 3-n-butyl-7-benzenesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CIV) (26.5%). The yield of unreacted starting material recovered and CIV isolated tend to suggest that benzenesulfonyl azide reacts with the amide carbonyl of the intermediate triazole formed by addition to the C_5-C_6 bond. Subsequent loss of nitrogen and cyclization would afford CIV on workup as shown in equation 15.



(15)

The infrared and nmr spectra of CIV were identical to those of the product obtained from reaction of 2-n-butyl-1,2-dihydropyridine (LVI) with benzenesulfonyl azide.

3.4.0.0.0 Broad spectrum pharmacological screening

The broad spectrum pharmacological screening of compounds LXXIII, LXXV, LXXIX, CIII, CIV, CVIII, CIX and CXII is currently in progress. The screening is being carried out under a "Screening Program for New Drug Type Discoveries" under an agreement between Canadian Patents and Developments Limited and Bio-Research Laboratories Limited.

The pharmacological tests on compounds LXXIII, LXXV and LXXIX have recently been completed.

The antimicrobial activity of the latter three compounds was determined using bacteria, yeast and fungi. Minimal Inhibitory Concentrations (MIC) in micrograms of compound per millilitre of media were interpreted as follows: bacteria; < 100 ug/ml (active), 100-500 ug/ml (slightly active), > 500 ug/ml (inactive), fungi and yeast; < 10 ug/ml (active), 10-500 ug/ml (slightly active) and > 500 ug/ml (inactive). Compound LXXIII exhibited slight activity against Bordatella bronchisepticus, Streptococcus faecalis and Bacillus subtilis. Compound LXXIII was not tested on fungi and yeast. Compound LXXV exhibited slight activity against Bord. bronch., Strept. faec. and Bacillus subt. as well as Trichophyton mentagrophytes, Microsporum gypseum, Candida albicans and Sacharomyces carlsbergensis. Compound LXXV was active in inhibiting growth of Staphlococcus aureus and

Aspergillus niger. Compound LXXIX was active in inhibiting growth of Bacillus subt..

The neuropharmacological profile of compound LXXIII was determined after intraperitoneal administration to Swiss Albino Mice. Compound LXXIII exhibited muscle relaxant and analgesic properties five minutes after intraperitoneal injection which lasted for more than one and one-half hours. No mortality was observed in mice used for this test. The analgesic activity exhibited by compound LXXIII after subcutaneous administration was determined using the phenylquinone writhing test. Administration of LXXIII (64 mg/kg body weight) reduced the phenylquinone induced writhing by 80%. In comparison, acetylsalicylic acic (50 mg/kg body weight) and dextropropoxyphene (56 mg/kg body weight) reduce phenylquinone writhing by 50%. After intravenous injection using Sprague - Dawley rats compound LXXIII exhibited a slight cardiovascular effect by increasing blood pressure and heart rate. Compound LXXIII did not produce mortality in any of the rats used for these tests.

The intraperitoneal administration of compound LXXV using mice produced central nervous system stimulation. Increased irritability, tail lashing, tremors and convulsions were observed five minutes after injection followed by a prolonged increase in irritability and decrease in spontaneous activity. No mortality was observed in the mice. Compound LXXV administered subcutaneously also exhibited antiinflammatory activity of short duration.

Compound LXXIX exhibited central nervous system stimulation after intraperitoneal injection. At the high dose administered (128 mg/kg) the mortality was 100%. Intravenous administration of LXXIX using rats

produced an elevation in blood pressure by 60% for less than fifteen minutes. Compound LXXIX exhibited analgesic activity equal to that of LXXIII when administered subcutaneously at a dose of 64 mg/kg body weight.

The analgesic properties of compounds LXXIII and LXXIX indicate the necessity for screening a variety of 2,7-diazabicyclo [4.1.0] hept-4-enes and piperidylidene-2-amides before a valid structure-activity relationship can be proposed. Compounds similar to LXXV may prove to be useful potential antimicrobial agents. One of these compounds (CIX) where the cyano group has been replaced by a sulfanilyl moiety is presently undergoing evaluation via the pharmacological screening program described.

4.0.0.0.0 EXPERIMENTAL

Melting points were determined with a Buchi capillary apparatus and are uncorrected. Ultraviolet spectra were recorded on a Unicam SP 1800 spectrometer using absolute ethanol as solvent. Infrared spectra (in potassium bromide unless otherwise noted) were taken on a Perkin Elmer 267 or Unicam SP 1000 spectrometer. Nuclear magnetic resonance spectra were recorded for solutions of deuterochloroform unless otherwise noted with TMS as the internal standard. The spectra were recorded on a Varian A 60, EM-360 A, HA-100 or HA-220 spectrometer. Mass spectra were measured with an AEI-MS-9 or MS-50 mass spectrometer and these exact mass measurements are used in lieu of elemental analysis. Quantitative analysis were effected with a Hewlett-Packard 5710A dual column gas chromatograph.

All anhydrous reactions were conducted in predried glassware under a positive nitrogen atmosphere. Dry nitrogen gas was obtained by passage through sulfuric acid, solid potassium hydroxide and then anhydrous calcium sulfate.

4.1.0.0.0 Solvents and reagents

Anhydrous reagent grade ether and tetrahydrofuran were boiled under reflux in the presence of lithium aluminum hydride for three to five hours and distilled in a closed system for immediate use.

Acetonitrile was purified by stirring in the presence of calcium hydride for two hours prior to distillation and storage under a nitrogen atmosphere.

Pyridine was dried by refluxing with calcium hydride prior to distillation and storage over potassium hydroxide.

n-Butyllithium was supplied by Alpha-Ventron as a 2.2 to 2.4 M solution in n-hexane and was assayed before use to determine the exact molarity.

Methanesulfonyl azide and benzenesulfonyl azide were prepared by reaction of methane(benzene)sulfonyl chloride with sodium azide using the method described by Stout[81]. N-acetylsulfanilyl azide was prepared as described by Curtis[82] and sulfanilyl azide was obtained by acid hydrolysis of N-acetylsulfanilyl azide as described by Cremlyn[83]. Hydrazoic acid was prepared using the procedure reported by Wolff[84]. Methoxycarbonyl azide was obtained using the method reported by Lindemann and Schulthesis[85].

N-methoxycarbonyl-2-n-butyl-1,2-dihydropyridine and N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine were prepared by reaction of methyl chloroformate with the corresponding organolithium - pyridine adducts using the procedure described by Giam, Knaus and Pasutto[49]. N-methoxycarbonyl-1,2-dihydropyridine and N-methanesulfonyl-1,2-dihydropyridine were obtained using the method reported by Fowler[26]. The preparation of N-acetyl-2-n-butyl-1,2-dihydropyridine is described below.

4.2.0.0.0 Reactions of electrophiles with N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and 2-n-butyl-1,2-dihydropyridine (LVI)

4.2.1.0.0 Preparation of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and 2-n-butyl-1,2-dihydropyridine (LVI)

General Procedure A

To a solution of n-butyllithium (8.89 ml of 2.25M, 0.02 mol) in 50 ml anhydrous ether, under a nitrogen atmosphere, pyridine (1.62 ml, 0.02 mol) was added dropwise with stirring at 0^{o}. The resulting dark brown solution containing N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (2.86 g, 0.02 mol) was allowed to stir 35 min at 0^{o} prior to use in subsequent reactions.

Water (0.36 ml, 0.02 mol) was added dropwise with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) in 50 ml of dry ether under a nitrogen atmosphere at 0^{o} to afford 2-n-butyl-1,2-dihydropyridine (LVI).

N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII)

4.2.2.1.1 From N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and ethyl acetate

General Procedure B

Ethyl acetate (0.914 ml, 0.0095 mol) was added dropwise with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (1.36 g, 0.0095 mol) in 50 ml of anhydrous ether under a nitrogen atmosphere at -77^{o}. The resulting solution was allowed to stir at

-77° for 20 minutes and after warming to room temperature, water (20 ml) was added. Extraction with chloroform (3x20 ml), drying (sodium sulfate) and removal of the solvent yielded a light yellow oil. Quantitative vpc analysis on a 1/8 inch x 20 inch column packed with 10% UCW-98 on WAW-DMCS (80-100 mesh) with a helium flow rate of 25 ml/min and a column temperature of 125° afforded 2-n-butylpyridine (LVIII) (0.011 g, 0.82%), retention time of 1.2 min, which showed ir and nmr spectra identical to those of an authentic sample; and N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) (1.743 g, 99.0%), retention time of 6.1 min; ir (neat): 1665 cm^{-1} (C=O); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.0 - 1.95 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 2.19 (s, 3, $COCH_3$), 5.07 (m, 1, C_2-H), 5.33 (m, 1, C_5-H), 5.67 (m, 1, C_3-H), 5.82 (m, 1, C_4-H), 6.50 (m, 1, C_6-H); mass calcd. for $C_{11}H_{17}NO$, 179.1310; found, 179.1310.

N-diethylphosphoryl-2-n-butyl-1,2-dihydropyridine (LIX)

4.2.2.2.1 From N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and diethylchlorophosphate

A solution of diethylchlorophosphate (3.28 g, 0.019 mol) in 5 ml dry ether was added dropwise with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (2.72 g, 0.019 mol) in 50 ml of dry ether under a nitrogen atmosphere at -77°. The resulting solution was maintained at -77° for 20 minutes and after warming to room temperature water (20 ml) was added. Extraction with chloroform (3x20 ml), drying (sodium sulfate) and removal of the solvent yielded

a brown oil which was subjected to preparative tlc using six 8 x 8 inch silica gel GFP 254 plates, 0.75 mm in thickness, with benzene - ether (1:1 v/v) as the development solvent. Extraction of the band with R_f 0.70 using methanol gave N-diethylphosphoryl-2-n-butyl-1,2-dihydropyridine (LIX) (3.54 g, 68.3%); ir: 1265 cm^{-1} (P=O); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.0 - 1.8 (m, 12, $\underline{CH_2CH_2CH_2}CH_3$, $O\text{-}CH_2\underline{CH_3}$), 4.0 (m, 5, C_2-H, $O\text{-}\underline{CH_2}CH_3$), 5.25 (m, 1, C_5-H), 5.50 (m, 1, C_3-H), 5.85 (m, 1, C_4-H), 6.1 (m, 1, C_6-H); mass calcd. for $C_{13}H_{24}NO_3P$, 273.14937; found, 273.1494.

4.2.2.2.2. From 2-n-butyl-1,2-dihydropyridine (LVI) and diethylchlorophosphate

A solution of diethylchlorophosphate (3.45 g, 0.020 mol) in 5 ml dry ether was added dropwise with stirring to a solution of 2-n-butyl-1,2-dihydropyridine (LVI) (2.74 g, 0.020 mol) in 50 ml of anhydrous ether under a nitrogen atmosphere at 25°. Triethylamine (2.42 g, 0.024 mol) was then added dropwise and the reaction allowed to proceed for 1 hr after which water (20 ml) was added. Extraction with chloroform (3x20 ml), drying (sodium sulfate) and removal of the solvent gave a yellow oil which was purified by preparative tlc as described under section 4.2.2.2.1 to give N-diethylphosphoryl-2-n-butyl-1,2-dihydropyridine (LIX) (0.92 g, 16.8%). Extraction of the band having R_f 0.62 gave 2-n-butylpyridine (LVIII) (0.241 g, 8.9%).

N-(N-cyclohexyl)carboxamido-2-n-butyl-1,2-dihydropyridine (LX) and 5-(N-cyclohexyl)carboxamido-2-n-butylpyridine (LXI)

4.2.2.2.3 From N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and cyclohexylisocyanate

Cyclohexylisocyanate (2.42 ml, 0.019 mol) was added dropwise with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (2.717 g, 0.019 mol) in 50 ml of anhydrous ether under a nitrogen atmosphere at -77°. The resulting solution was allowed to stir at -77° for 20 minutes and after warming to room temperature water (20 ml) was added. Extraction with chloroform (3x20 ml), drying (sodium sulfate) and removal of the solvent gave a viscous brown oil which was separated by preparative tlc on six 8 x 8 inch silica gel GFP 254 plates, 0.75 mm in thickness, using benzene-ethyl acetate (1:3 v/v) as the developing solvent. Extraction of the band having R_f 0.95 using warm methanol afforded N-(N-cyclohexyl)carboxamido-2-n-butyl-1,2-dihydropyridine (LX) (0.846 g, 17%); ir (neat): 3340 cm^{-1} (NH), 1630 cm^{-1} (C=O); nmr: δ 0.8 - 2.05 (m, 21, C_4H_9, C_6H_{11}, NH, exchanges with D_2O), 4.66 (m, 1, C_2-H), 5.34 (m, 1, C_5-H), 5.64 (m, 1, C_3-H), 5.98 (m, 1, C_4-H), 6.4 (m, 1, C_6-H); mass calcd. for $C_{16}H_{26}N_2O$, 262.2045; found, 262.2045. Extraction of the band having R_f 0.65 yielded 5-(N-cyclohexyl)carboxamido-2-n-butylpyridine (LXI) (0.692 g, 14%), mp 103-104°; ir ($CHCl_3$); 3435 cm^{-1} (NH), 1650 cm^{-1} (C=O); nmr: δ 0.94 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 2.1 (m, 15, C_6H_{11}, $CH_2\underline{CH_2CH_2}CH_3$), 2.29 (broad s, 1, NH, exchanges with deuterium oxide), 2.82 (t(J = 7Hz), 2, $\underline{CH_2}CH_2CH_2CH_3$), 7.22 (d ($J_{3,4}$ = 7.5 Hz), 1, C_3-H), 8.0 (d($J_{3,4}$ = 7.5 Hz) of d ($J_{4,6}$ = 2.5 Hz),

1, C_4-H), 8.84 (d($J_{4,6}$ = 2.5 Hz), 1, H_6); mass calcd. for $C_{16}H_{24}N_2O$, 260.1888; found, 260.1892.

2-n-butyl-5-aminopyridine (LXII) and 6,6'-di-n-butyl-1,2,3,6-tetrahydro-2,3'-dipyridyl (LXIII)

4.2.2.3.1 From N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and chloramine

A solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (4.29 g, 0.03 mol) in 50 ml of anhydrous ether was added slowly with stirring to a solution of chloramine (0.515 g, 0.01 mol) in 200 ml of dry ether under a nitrogen atmosphere at -77°. The temperature was maintained at -77° for 1 hr and after warming to 25°, water (50 ml) was added. Extraction with chloroform (3x20 ml), drying (sodium sulfate) and removal of the solvent gave a yellow oil which was subjected to preparative tlc on six 8 x 8 inch silica gel GFP 254 plates, 0.75 mm in thickness, with benzene - methanol (7:1 v/v) as the development solvent. Extraction with warm methanol (50 ml) of the fraction with R_f of 0.36 gave 2-n-butyl-5-aminopyridine (LXII) (0.861 g, 57.4%); ir (neat): 3200 and 3320 cm^{-1} (NH_2); nmr: δ 0.9 (t(J = 7 Hz), 3, CH_3), 1.1 - 2.0 (m, 4, $CH_2\underline{CH_2}\underline{CH_2}CH_3$), 2.67 (t(J = 7 Hz), 2, $\underline{CH_2}CH_2CH_2$-CH_3), 3.46 (br s, 2, NH_2, exchanges with deuterium oxide), 6.86 (m, 2, C_3-H, C_4-H), 8.0 (m, 1, C_6-H); mass calcd. for $C_9H_{14}N_2$, 150.11570; found, 150.11615. Extraction of the band with R_f 0.62 afforded 6,6'-di-n-butyl-1,2,3,6-tetrahydro-2,3'-dipyridyl (LXIII) (1.238 g, 30.3%); ir (neat): 3260 cm^{-1} (NH); nmr: δ 0.9 (t(J = 7 Hz), 6, CH_3), 1.1 - 2.0 (m, 10, C_6-$\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_3$ and $C_{6'}$-$CH_2\underline{CH_2}\underline{CH_2}CH_3$), 2.2 (m, 2, C_3-H),

2.6 (br s, 1, NH, exchanges with deuterium oxide), 2.76 (t(J = 7 Hz), 2, $C_{6'}$-$\underline{CH_2}CH_2CH_2CH_3$), 3.35 (m, 1, C_6-H), 4.0 (t(J = 7 Hz), 1, C_2-H), 5.8 (m, 2, C_4-H, C_5-H), 7.08 (d($J_{4',5'}$ = 8 Hz), 1, $C_{5'}$-H), 7.62 (d($J_{4',5'}$ = 8 Hz) of d($J_{2',4'}$ = 2.5 Hz), 1, $C_{4'}$-H), 8.3 (d($J_{2',4'}$ = 2.5 Hz), 1, $C_{2'}$-H); mass calcd. for $C_{18}H_{28}N_2$, 272.22525; found, 272.22517. Extraction of the fraction having R_f 0.75 gave rise to 2-n-butylpyridine (LVIII) (0.108 g, 2.7%) which showed ir and nmr spectra identical to those of an authentic sample.

Reaction of XXX (2.86 g, 0.02 mol) with chloramine (1.03 g, 0.02 mol) as described above afforded LVIII (0.212 g, 7.9%), LXII (0.69 g, 23%) and LXIII (0.981 g, 36.1%).

6,6'-di-n-butyl-3,3'-dipyridyl (LXIV)

4.2.2.4.1 From N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and cyanogen bromide

Cyanogen bromide (1.06 g, 0.01 mol) in 10 ml of dry ether was added dropwise with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (1.43 g, 0.01 mol) in 50 ml of dry ether under a nitrogen atmosphere at -77°. The resulting solution containing the precipitated lithium bromide was maintained at -77° for 1 hr and after warming to 25° water (20 ml) was added. Extraction with chloroform (3x20 ml), drying (sodium sulfate) and removal of the solvent gave a brown oil which was separated by preparative tlc on six 8 x 8 inch silica gel GFP 254 plates, 0.75 mm in thickness, using benzene - ether (2:1 v/v) as the development solvent. Extraction of the band having R_f 0.32 using warm methanol (50 ml) afforded

6,6'-di-n-butyl-3,3'-dipyridyl (LXIV) (0.422 g, 26.4%), mp 5-8°; nmr: δ 0.9 (t(J = 7 Hz), 6, CH_3), 1.1 - 2.1 (m, 8, $-CH_2\underline{CH_2}\underline{CH_2}CH_3$), 2.8 (t(J = 7 Hz), 4, $-\underline{CH_2}CH_2CH_2CH_3$), 7.14 (d($J_{4,5} = J_{4',5'} = 8$ Hz), 2, C_5-H, $C_{5'}$-H), 7.68 (d($J_{4,5} = J_{4',5'} = 8$ Hz) of d($J_{2,4} = J_{2',4'} = 2.5$ Hz), 2, C_4-H, $C_{4'}$-H), 8.61 (d($J_{2,4} = J_{2',4'} = 2.5$ Hz), 2, C_2-H, $C_{2'}$-H); mass calcd. for $C_{18}H_{24}N_2$, 268.1940; found, 268.1932. Extraction of the band with R_f 0.56 gave rise to 2-n-butylpyridine (LVIII) (0.3 g, 22.2%).

4.2.2.4.2 From 2-n-butyl-1,2-dihydropyridine (LVI) and cyanogen bromide

Water (0.35 ml, 0.0193 mol) was added dropwise with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (2.76 g, 0.0193 mol) in 50 ml of dry ether under a nitrogen atmosphere at 0°. The solution was allowed to stand at 0° for 15 min before returning to 25°. A solution of cyanogen bromide (2.05 g, 0.0193 mol) in 10 ml of dry ether was added and the reaction allowed to proceed for 1 hr after which water (20 ml) was added. The reaction was completed and preparative tlc effected as described under section 4.2.2.4.1 above to yield 6,6'-di-n-butyl-3,3'-dipyridyl (LXIV) (0.238 g, 7.2%) and 2-n-butylpyridine (LVIII) (0.896 g, 27.1%).

2-n-butyl-5-bromopyridine (LXV)

4.2.2.4.3 From N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and cyanogen bromide using an inverse addition procedure

A solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (2.86 g,

0.02 mol) in 50 ml of dry ether was added slowly to a solution of cyanogen bromide (10.59 g, 0.10 mol) in 25 ml of dry ether under a nitrogen atmosphere at -77°. The reaction was completed as described under section 4.2.2.4.1 above to afford a brown oil which was subjected to preparative tlc using six 8 x 8 inch silica gel GFP 254 plates, 0.75 mm in thickness, with benzene - ether (3:1 v/v) as the development solvent. Extraction of the band with R_f 0.67 using warm methanol (50 ml) gave 2-n-butyl-5-bromopyridine (LXV) (0.638 g, 14.9%); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 2.0 (m, 4, $CH_2\underline{CH_2CH_2}CH_3$), 2.71 (t(J = 7 Hz), 2, $\underline{CH_2}CH_2CH_2CH_3$), 6.98 (d($J_{3,4}$ = 8 Hz), 1, C_3-H), 7.63 (d($J_{3,4}$ = 8 Hz) of d($J_{4,6}$ = 2.5 Hz), 1, C_4-H), 8.49 (d($J_{4,6}$ = 2.5 Hz), 1, C_6-H). Extraction of the fraction having R_f 0.78 afforded 2-n-butylpyridine (LVIII) (0.876 g, 32.5%).

4.2.2.5.1 From N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and N-bromosuccinimide using an inverse addition procedure

A solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (2.86 g, 0.02 mol) in 50 ml of dry ether was added dropwise with vigorous stirring to a suspension of N-bromosuccinimide (17.8 g, 0.1 mol) in 100 ml of dry ether under an atmosphere of nitrogen at -77°. The reaction was allowed to proceed for 2 hr at -77° and then completed according to the procedure described under section 4.2.2.4.1 to yield a reddish semi-solid which was purified by preparative tlc as under section 4.2.2.4.3 above to give 2-n-butyl-5-bromopyridine (LXV) (0.445 g, 10.5%) and 2-n-butylpyridine (LVIII) (0.223 g, 8.2%).

4.2.2.6.1 Reaction of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) with N-methanesulfonylpyridinium chloride

A solution of N-methanesulfonylpyridinium chloride (3.87 g, 0.02 mol) in 50 ml dry tetrahydrofuran was added slowly with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (2.86 g, 0.02 mol) in 50 ml of dry ether under a nitrogen atmosphere at -77°. The reaction was completed as described under section 4.2.2.3.1 to afford an orange oil which was separated on six 8 x 8 inch silica gel GFP 254 plates, 0.75 mm in thickness, using benzene - ether (1:9 v/v) as the development solvent. Extraction of the fractions having R_f's of 0.54 and 0.72 afforded 6,6'-di-n-butyl-3,3'-dipyridyl (LXIV) (0.369 g, 6.9%) and 2-n-butylpyridine (LVIII) (0.562 g, 20.8%), respectively.

2-n-butyl-5-methanesulfonylpyridine (LXVI)

4.2.2.6.2 From 2-n-butyl-1,2-dihydropyridine (LVI) and N-methanesulfonylpyridinium chloride

A solution of N-methanesulfonylpyridinium chloride (3.87 g, 0.02 mol) in 50 ml of dry tetrahydrofuran was added slowly with stirring to a solution of 2-n-butyl-1,2-dihydropyridine (LVI) (2.74 g, 0.02 mol) in 50 ml of dry ether under a nitrogen atmosphere at 25°. The reaction was allowed to proceed for 30 min and then completed as described under section 4.2.2.3.1 to afford a brown oil which was subjected to preparative tlc on six 8 x 8 inch silica gel GFP 254 plates, 0.75 mm in thickness, using benzene - ethyl acetate (1:2 v/v)

as the develoment solvent. Extraction of the band having R_f 0.54 gave 2-n-butyl-5-methanesulfonylpyridine (LXVI) (0.233 g, 11.2%), mp 45-47°; ir: 1155 and 1295 cm^{-1} (SO_2); nmr: δ 0.98 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.2 - 2.1 (m, 4, $CH_2\underline{CH_2CH_2}CH_3$), 2.92 (t(J = 7 Hz), 2, $\underline{CH_2}CH_2CH_2CH_3$), 3.12 (s, 3, SO_2CH_3), 7.35 (d($J_{3,4}$ = 8 Hz), 1, C_3-H), 8.12 (d($J_{3,4}$ = 8 Hz) of d($J_{4,6}$ = 2 Hz), 1, C_4-H), 9.0 (d($J_{4,6}$ = 2 Hz), 1, C_6-H); mass calcd. for $C_{10}H_{15}NO_2{}^{32}S$, 213.0824; found, 213.0831. Extraction of the fraction with R_f 0.75 gave 2-n-butylpyridine (LVIII) (0.793 g, 39.8%).

2-n-butyl-5-phenylselenylpyridine (LXVII)

4.2.2.7.1 From N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and phenylselenyl chloride

A solution of phenylselenyl chloride (1.82 g, 0.01 mol) in 5 ml of dry ether was added dropwise with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (1.43 g, 0.01 mol) in 50 ml of dry ether under a nitrogen atmosphere at -77°. The reaction was allowed to stir for 30 min; triethylamine (0.01 mol) was added followed by further stirring at -77° for 30 min. The reaction was completed by the procedure given under section 4.2.2.3.1 to yield an orange oil. Quantitative vpc analysis on a 1/8 x 20 inch column packed with 10% UCW-98 on WAW-DMCS (80-100 mesh) with a helium flow rate of 25 ml/min and a column temperature of 125° gave 2-n-butylpyridine (LVIII) (0.157 g, 12.2%), retention time of 1.2 min; and at 200° afforded 2-n-butyl-5-phenylselenylpyridine (LXVII) (0.449 g, 16.3%), retention

time of 5.8 min; nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.0 - 2.0 (m, 4, $CH_2\underline{CH_2CH_2}CH_3$), 2.7 (t(J = 7 Hz), 2, $\underline{CH_2}CH_2CH_2CH_3$), 6.8 - 7.5 (m, 7, C_6H_5, C_3-H, C_4-H), 8.53 (d($J_{4,6}$ = 2 Hz), 1, C_6-H); mass calcd. for $C_{15}H_{17}N^{80}Se$, 291.0526; found, 291.0525.

4.2.2.7.2 From 2-n-butyl-1,2-dihydropyridine (LVI) and phenylselenyl chloride

Reaction of 2-n-butyl-1,2-dihydropyridine (LVI) (1.37 g, 0.01 mol) with phenylselenyl chloride (1.82 g, 0.01 mol) at 25° and completion of the reaction as described under section 4.2.2.7.1 above afforded 2-n-butylpyridine (LVIII) (0.171 g, 13.4%) and 2-n-butyl-5-phenylselenylpyridine (LXVII) (0.493 g, 17.8%).

5-methyl-2-n-butylpyridine (LXVIII)

4.2.2.8.1 From N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and methyl p-toluenesulfonate

Methyl p-toluenesulfonate (1.86 g, 0.01 mol) was added dropwise with stirring to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (1.43 g, 0.01 mol) in 50 ml of dry ether under a nitrogen atmosphere at -77°. The reaction was completed according to the procedure described under section 4.2.2.3.1 to give a brown oil. Quantitative vpc analysis on a 1/8 x 20 inch column packed with 10% UCW-98 on WAW-DMCS (80-100 mesh) with a helium flow rate of 25 ml/min and a column temperature of 125° afforded 2-n-butylpyridine (LVIII) (0.076 g, 5.9%), retention time 1.2 min; and 5-methyl-2-n-butylpyridine (LXVIII) (0.774 g, 54.7%) retention time 2.0 min; nmr:

δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.0 - 2.0 (m, 4, $CH_2\underline{CH_2CH_2}CH_3$), 2.24 (s, 3, CH_3), 2.74 (t(J = 7 Hz), 2, $\underline{CH_2}CH_2CH_2CH_3$), 6.95 (d($J_{3,4}$ = 8 Hz), 1, C_3-H), 7.33 (d($J_{3,4}$ = 8 Hz) of d ($J_{4,6}$ = 2 Hz), 1, C_4-H), 8.28 (d($J_{4,6}$ = 2 Hz), 1, C_6-H); mass calcd. for $C_{10}H_{15}N$, 149.1205; found, 149.1181. Anal. Calcd. for $C_{10}H_{15}N$: C,80.5; H, 10.1. Found: C, 80.9; H, 10.4.

4.2.2.8.2 From 2-n-butyl-1,2-dihydropyridine (LVI) and methyl p-toluenesulfonate

Methyl p-toluenesulfonate (1.86 g, 0.01 mol) was added to a solution of 2-n-butyl-1,2-dihydropyridine (LVI) (1.37 g, 0.01 mol) in 50 ml of dry ether under a nitrogen atmosphere at 25° and the reaction was completed and subjected to quantitative vpc analysis as described under section 4.2.2.8.1 to afford 2-n-butylpyridine (LVIII) (0.19 g, 14.8%) and 5-methyl-2-n-butylpyridine (LXVIII) (0.23 g, 16.1%).

4.2.2.8.3 From N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and methyl trifluoromethanesulfonate

Methyl trifluoromethanesulfonate (1.56 g, 0.01 mol) was added to a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (1.43 g, 0.01 mol) in 50 ml of dry ether at -77° and the reaction was completed and subjected to quantitative vpc analysis as described under section 4.2.2.8.1 to yield 2-n-butylpyridine (LVIII) (0.068 g, 5.3%) and 5-methyl-2-n-butylpyridine (LXVIII) (0.605 g, 42.7%).

4.2.2.8.4 From 2-n-butyl-1,2-dihydropyridine (LVI) and methyl trifluoromethanesulfonate

Methyl trifluoromethanesulfonate (1.56 g, 0.01 mol) was added to a solution of 2-n-butyl-1,2-dihydropyridine (LVI) (1.37 g, 0.01 mol) in 50 ml of dry ether at 25°. The reaction was completed and subjected to quantitative vpc analysis as described under section 4.2.2.8.1 to yield 2-n-butylpyridine (LVIII) (0.21 g, 16.4%) and 5-methyl-2-n-butylpyridine (LXVIII) (0.28 g, 19.7%).

5-endo-diethylphosphoryl-6-exo-n-butyl-2,3,5-triazabicyclo [2.2.2] oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide (LXIX)

4.3.1.0.0 From N-diethylphosphoryl-2-n-butyl-1,2-dihydropyridine (LIX) and 4-phenyl-1,2,4-triazoline-3,5-dione

A solution of N-diethylphosphoryl-2-n-butyl-1,2-dihydropyridine (LIX) (0.123 g, 0.45 mmol) in 5 ml dry dichloromethane was added dropwise with stirring to a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (0.079 g, 0.45 mmol) in 20 ml of dry dichloromethane under a nitrogen atmosphere at 25°. Evaporation of the solvent gave 5-endo-diethylphosphoryl-6-exo-n-butyl-2,3,5-triazabicyclo[2.2.2]oct-7-ene-2,3-endo-dicarboxylic acid N-phenylimide (LXIX) (0.196 g, 97%) as a light yellow oil; ir: 1770 and 1720 cm^{-1} (C=O) and 1250 cm^{-1} (P=O); nmr (DMSO-d_6): δ 0.70 - 1.90 (m, 15, CH_3, C_4H_9), 4.02 (q(J = 7 Hz), 4, $\underline{CH_2}CH_3$), 5.08 (m, 1, C_6-H), 5.76 - 6.00 (m, 2, C_7-H, C_1-H), 6.56 (m, 1, C_8-H), 6.87 (m, 1, C_4-H), 7.3 - 7.65 (m, 5, Ph); mass calcd. for $C_{21}H_{29}N_4O_5P$, 448.1877; found, 448.1873.

4.4.0.0.0 Reactions of 1,2-dihydropyridines with organic azides

4.4.1.1.0 Preparation of cyanogen azide

General Procedure C

Cyanogen azide was prepared using the procedure of Marsh[86]. Cyanogen bromide (2.65 g, 0.025 mol) in 25 ml dry acetonitrile was added slowly with vigorous stirring to a suspension of sodium azide (8.12 g, 0.125 mol) in 75 ml dry acetonitrile under a nitrogen atmosphere at 0°. After stirring for 1 hr at 0° the reaction mixture was warmed slowly to 25° during a 2 hr period. The reaction mixture was maintained at 25° for 1 hr after which the supernatant was transferred using a syringe to a second reaction vessel under a nitrogen atmosphere.

4.4.1.2.0 Preparation of lithium hydroxide free 2-n-butyl-1,2-dihydropyridine (LVI)

General Procedure D

To a solution of N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) (4.29 g, 0.03 mol) in 100 ml anhydrous ether under a nitrogen atmosphere water (2.0 ml, 0.11 mol) was added dropwise with stirring at 0°. The reaction was allowed to proceed for 10 min, anhydrous sodium sulfate (25 g) was added and the mixture was stirred for an additional 15 min at 0°. The solution was then allowed to sit without agitation for 5 min after which an aliquot of the supernatant containing the required amount of 2-n-butyl-1,2-dihydropyridine (LVI) was removed

using a syringe under a nitrogen atmosphere.

2,2'-dithiodipyridyl · 2HBr (LXXII) and 2-pyridylthiocyanide (LXXI)

4.4.2.1.1 From 2-mercaptopyridine and cyanogen azide

A solution of cyanogen azide prepared from cyanogen bromide (2.55 g, 0.025 mol) and sodium azide (1.625 g, 0.025 mol) in 100 ml dry acetonitrile, as described under Procedure C was added slowly with stirring to a solution of 2-mercaptopyridine (2.22 g, 0.02 mol) in 100 ml dry acetonitrile under a nitrogen atmosphere at 0°. The reaction was allowed to proceed for 30 min and after warming to 25° the solvent was removed in vacuo. Recrystallization from chloroform (100 ml) afforded 2,2'-dithiodipyridyl dihydrobromide (LXXII) (1.7 g, 44.5%); nmr (D_2O): δ 7.83 - 8.6 (m, 6, C_3-H, C_4-H, C_5-H, $C_{3'}$-H, $C_{4'}$-H, $C_{5'}$-H), 8.88 (m, 2, C_6-H, $C_{6'}$-H). Anal. Calcd. for $C_{10}H_{10}N_2S_2Br$: C, 31.43; H, 2.62; N, 7.33. Found: C, 31.29; H, 2.75; N, 7.34. Evaporation of the solvent gave 2-pyridylthiocyanide (LXXI) as a light yellow oil (1.46 g, 53.6%); ir(neat): 2130 cm^{-1} (C≡N); nmr: δ 7.08 - 7.93 (m, 3, C_3-H, C_4-H, C_5-H), 8.48 (m, 1, C_6-H); mass calcd. for $C_6H_4N_2S$, 136.0096; found, 136.0093.

A solution of 2,2'-dithiodipyridyl dihydrobromide (LXXII) (0.45 g, 1.18 mmol) in 25 ml of water was adjusted to pH 12 using 10% NaOH solution. The precipitate was then filtered off yielding 2,2'-dithiodipyridyl (0.26 g, 100%) which showed nmr and ir spectra identical to those of an authentic sample.

4.4.2.1.2 From 2-mercaptopyridine and cyanogen bromide

A solution of cyanogen bromide (1.06 g, 0.01 mol) in 50 ml dry acetonitrile was added slowly with stirring to a solution of 2-mercaptopyridine (1.11 g, 0.01 mol) in 50 ml dry acetonitrile under a nitrogen atmosphere at 0^{o}. After the reaction had proceeded for 1 hr at 0^{o} it was warmed to room temperature and the solvent was removed. Recrystallization from chloroform (100 ml) yielded 2,2'-dithiodipyridyl dihydrobromide (LXXII) (1.84 g, 96.3%) and 2-pyridylthiocyanide (LXXI) (0.046 g, 3.4%).

4.4.2.2.1 Reaction of 2-mercaptopyridine-N-oxide with cyanogen azide

A solution of 2-mercaptopyridine-N-oxide (2.54 g, 0.02 mol) in 25 ml dry acetonitrile was added slowly with stirring to a solution of cyanogen azide prepared from cyanogen bromide (2.65 g, 0.025 mol) in 100 ml dry acetonitrile under a nitrogen atmosphere at 0^{o}. The reaction mixture was maintained at 0^{o} for 30 min prior to warming to room temperature and solvent removal in vacuo. Recrystallization from chloroform (100 ml) yielded an unidentified solid (2.66 g) mp: 163^{o} (decomp.), ir: 2150, 1575, 1460, 1415, 1215 and 1195 cm^{-1}; nmr (D_2O) δ 7.67 (m), 8.5 (m) (ratio of areas 3:1); analysis found: C, 36.42; H, 3.45. Evaporation of the chloroform yielded an unidentifiable orange oil (0.503 g), ir: 1460, 1420 cm^{-1}; nmr δ 7.5 (m), 8.25 (m), (ratio of areas is 3:1), analysis found: C, 38.98; H, 2.80.

3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII)

4.4.2.3.1 From 2-n-butyl-1,2-dihydropyridine (LVI) and cyanogen azide

A solution of 2-n-butyl-1,2-dihydropyridine (LVI) (2.74 g, 0.02 mol) in 67 ml dry ether prepared as described under Procedure D, was added slowly with stirring to a solution of cyanogen azide prepared, as described under Procedure C, from cyanogen bromide (2.65 g, 0.025 mol) and sodium azide (8.125 g, 0.125 mol) in 100 ml acetonitrile under a nitrogen atmosphere at 0^{o}. The reaction was allowed to proceed at 0^{o} for 1 hr and then warmed to 25^{o}. Removal of the solvent in vacuo gave a light orange solid. Recrystallization from 100 ml ether - hexane (1:4 v/v) afforded 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII) (3.54 g, 100%); mp: 75^{o}; ir: 3225 cm^{-1} (NH), 2180 cm^{-1} (C≡N) and 1605 cm^{-1} (C=C); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.9 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 3.21 (m, 1, C_6-H), 3.3 (m, 1, C_1-H), 4.17 (m, 1, C_3-H), 5.8 (m, 2, C_4-H, C_5-H), 8.63 (broad s, 1, NH, exchanges with deuterium oxide); mass calcd. for $C_{10}H_{15}N_3$), 177.1266; found, 177.1265.

6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXV)

4.4.2.3.2 From 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII).

Elution of 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII) (0.406 g, 2.3 mmol) from a 2.5 x 33 cm neutral alumina column (Brockman Activity 1) using ethyl acetate (300 ml) gave a white solid

which was subjected to preparative tlc on six 8 x 8 inch silica gel G plates, 0.75 mm in thickness, using ether -ethyl acetate (9:1 v/v) as development solvent. Extraction of the fraction having R_f 0.8 with 50 ml warm methanol gave 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXV)(0.321 g, 79%); mp: 61°; ir: 3240 cm^{-1} (NH), 2180 cm^{-1} (C≡N), 1645 cm^{-1} (C=C) and 1575 cm^{-1} (C=N); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 2.0 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 2.4 (m, 2, C_5-H), 3.6 (m, 1, C_6-H), 6.3 (m, 1, C_3-H), 6.65 (m, 1, C_4-H), 7.45 (m, 1, NH, exchanges with D_2O); mass calcd. for $C_{10}H_{15}N_3$, 177.1266; found, 177.1265.

<u>6-n-butylpiperidylidene-2-cyanamide (LXXIXa) and 6-n-butyl-3,4,5,6-tetrahydropyridyl-2-cyanamide (LXXIXb)</u>

4.4.2.3.3 From 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII) or 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXV)

Hydrogenation of 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII) (0.12g, 0.68 mmol) or 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXV) (0.123 g, 0.695 mmol) in 75 ml methanol using 45 mg 10% palladium on charcoal and hydrogen gas at 35 psi for 4 hr at 25° followed by filtration and removal of the solvent <u>in vacuo</u> afforded the tautomeric mixture 6-n-butylpiperidylidene-2-cyanamide (LXXIXa) and 6-n-butyl-3,4,5,6-tetrahydropyridyl-2-cyanamide (LXXIXb) in quantitative yield (0.121 g and 0.124 g respectively); ir: 3240 cm^{-1} (LXXIXa) (NH), 3120 cm^{-1} (LXXIXb)

(NH), 2180 cm^{-1} (C≡N), 1645 cm^{-1} (LXXIXb) (C=N) and 1605 cm^{-1} (LXXIXa) (C=N); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 2.3 (m, 10, $\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_3$, C_4-H, C_5-H), 2.7 (m, 2, C_3-H), 3.4 (m, 1, C_6-H), 8.0 (broad s, 1, NH, exchanges with D_2O); mass calcd. for $C_{10}H_{17}N_3$, 179.1422; found, 179.1418.

3-phenyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIV)

4.4.2.4.1 From 2-phenyl-1,2-dihydropyridine and cyanogen azide

A solution of 2-phenyl-1,2-dihydropyridine (3.1 g, 0.02 mol) in 100 ml dry tetrahydrofuran was added slowly with stirring to a solution of cyanogen azide prepared, as described under Procedure C, from cyanogen bromide (2.65 g, 0.025 mol) and sodium azide (8.125 g, 0.125 mol) in 100 ml acetonitrile under a nitrogen atmosphere at 0^o. The reaction was maintained at 0^o for 1 hr and after warming to 25^o removal of the solvent in vacuo yielded an orange solid. Recrystallization from 100 ml ether - hexane (1:4 v/v) yielded 3-phenyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIV) (3.94 g, 100%); mp: 147^o; ir: 3235 cm^{-1} (NH), 2180 cm^{-1} (C≡N) and 1610 cm^{-1} (C=C); nmr: δ 3.2 (m, 1, C_6-H), 3.3 (m, 1, C_1-H), 5.08 (m, 1, C_3-H), 5.77 (m, 2, C_4-H, C_5-H), 7.26 (m, 5, C_6H_5), 7.82 (broad s, 1, NH, exchanges with D_2O); mass calcd. for $C_{12}H_{11}N_3$, 197.0953; found, 197.0954.

6-phenyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXVIII)

4.4.2.4.2 From 3-phenyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIV)

A suspension of 5 g neutral alumina (Brockman Activity I) in 25 ml chloroform containing 3-phenyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIV) (0.216 g, 1.1 mmol) was stirred at 25° for 72 hr. Extraction with ethyl acetate (100 ml) and removal of the solvent in vacuo afforded 6-phenyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXVIII) (0.218 g, 100%); mp: 129°; ir: 3190 cm^{-1} (NH), 2180 cm^{-1} (C≡N), 1650 cm^{-1} (C=C) and 1580 cm^{-1} (C=N); nmr: δ 2.6 (m, 2, C_5-H), 4.65 (m, 1, C_6-H), 6.35 (m, 1, C_3-H), 6.56 (m, 1, C_4-H), 7.25 (m, 5H, C_6H_5), 8.52 (broad s, 1, NH, exchanges with D_2O); mass calcd. for $C_{12}H_{11}N_3$, 197.0953; found, 197.0943.

6-phenylpiperidylidene-2-cyanamide (LXXXIa) and 6-phenyl-3,4,5,6-tetrahydropyridyl-2-cyanamide (LXXXIb)

4.4.2.4.3 From 3-phenyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIV) or 6-phenyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXVIII)

Hydrogenation of 3-phenyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIV) (0.132 g, 0.67 mmol) or 6-phenyl-1,2,5,6-tetrahydropyridylidene-2-cyanamide (LXXVIII) (0.137 g, 0.695 mmol) in 75 ml methanol using 45 mg 10% palladium on charcoal and hydrogen gas at 35 psi for 4 hr at 25° followed by filtration and removal of the solvent in vacuo afforded the tautomeric mixture of 6-phenylpiperidylidene-2-cyanamide (LXXXIa) and 6-phenyl-3,4,5,6-tetrahydropyridyl-2-cyanamide

(LXXXIb) in quantitative yield; ir: 3230 cm^{-1} (NH) (LXXXIa), 3140 cm^{-1} (NH) (LXXXIb), 2170 cm^{-1} (C≡N), 1600 cm^{-1} (C=N) (LXXXIb) and 1575 cm^{-1} (C=N) (LXXXIa); nmr: δ 1.5 - 2.3 (m, 4, C_4-H, C_5-H), 2.7 (m, 2, C_3-H), 4.6 (m, 1, C_6-H), 7.3 (m, 5, C_6H_5), 7.45 (broad s, 1, NH, exchanges with D_2O); mass calcd. for $C_{12}H_{13}N_3$, 199.1110; found, 199.1100.

6-phenyl-2-piperidone (LXXXII)

4.4.2.4.4 From 6-phenylpiperidylidene-2-cyanamide (LXXXIa) and 6-phenyl-3,4,5,6-tetrahydropyridyl-2-cyanamide (LXXXIb)

A solution of the tautomeric mixture of 6-phenylpiperidylidene-2-cyanamide (LXXXIa) and 6-phenyl-3,4,5,6-tetrahydropyridyl-2-cyanamide (LXXXIb) (0.2 g, 1.0 mmol) and 10 ml 10% sulfuric acid in 100 ml methanol was heated under reflux at 64° for 20 hr. The solution was neutralized to pH 7 using 10% aqueous sodium hydroxide, filtered and the solution was heated *in vacuo* to remove the methanol. Extraction of the remaining aqueous mother liquor with chloroform (3 x 50 ml), drying (sodium sulfate) and removal of the solvent *in vacuo* afforded a tan colored solid. Recrystallization from petroleum ether (bp 30°-60°) gave 6-phenyl-2-piperidone (LXXXII) (0.068 g, 38.7%); mp: 137°; ir: 3180 cm^{-1} (NH) and 1640 cm^{-1} (C=O); nmr: δ 1.5 - 2.1 (m, 4, C_4-H, C_5-H), 2.27 (m, 2, C_3-H), 4.4 (m, 1, C_6-H), 6.8 (m, 1, NH, exchanges with D_2O), 7.21 (m, 5, C_6H_5); mass calcd. for $C_{11}H_{13}NO$, 175.0997; found, 175.1001.

Syn-N-methoxycarbonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXIIIa) and anti-N-methoxycarbonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXIIIb)

4.4.2.5.1 From N-methoxycarbonyl-1,2-dihydropyridine and cyanogen azide

General Procedure E

A solution of N-methoxycarbonyl-1,2-dihydropyridine (2.78 g, 0.02 mol) in 50 ml of dry ether was added with stirring to a solution of cyanogen azide prepared from cyanogen bromide (2.65 g, 0.025 mol) and sodium azide (8.12 g, 0.125 mol) in 100 ml dry acetonitrile under a nitrogen atmosphere at 25°. The reaction was allowed to proceed for 20 hr at 25°. Filtration and removal of the solvent *in vacuo* gave a black semi-solid which was partitioned between chloroform (100 ml) and water (100 ml). The chloroform fraction was washed with water (50 ml) and the combined water fractions extracted with chloroform (2x75 ml). The chloroform extracts were dried (sodium sulfate) and the solvent removed *in vacuo* to yield a black semi-solid which was subjected to preparative tlc on ten 8 x 8 inch silica gel G plates, 0.75 mm in thickness, using benzene - ethyl acetate (2:1 v/v) as the development solvent. Extraction with 50 ml warm methanol of the fraction having R_f 0.95 gave N-methoxycarbonyl-1,2-dihydropyridine (0.676 g, 24.3%). Extraction of the band with R_f 0.47 afforded a 1:1 mixture of *syn*-N-methoxycarbonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXIIIa) and *anti*-N-methoxycarbonyl-1,2,3,4-tetrahydro-

pyridylidene-4-cyanamide (LXXXIIIb) (0.744 g, 20.8%); ir: 2180 cm^{-1} (C≡N), 1730 cm^{-1} (C=O), 1590 cm^{-1} (C=N) and 1560 cm^{-1} (C=C); nmr: (DMSO-d_6) δ 2.74 (LXXXIIIb) and 2.95 (LXXXIIIa) (t($J_{2,3}$ = 7.5 Hz), 2, C_3-H), 3.81 (s, 3, OCH_3), 3.90 (t($J_{2,3}$ = 7.5 Hz), 2, C_2-H), 5.59 (LXXXIIIa) and 5.85 (LXXXIIIb) (d($J_{5,6}$ = 8 Hz), 1, C_5-H), 7.90 (LXXXIIIb) and 7.95 (LXXXIIIa) (d($J_{5,6}$ = 8 Hz), 1, C_6-H); mass calcd. for $C_8H_9N_3O_2$, 179.0694; found, 179.0694.

Syn-N-methanesulfonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXVIIa) and anti-N-methanesulfonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXVIIb)

4.4.2.6.1 From N-methanesulfonyl-1,2-dihydropyridine and cyanogen azide

A solution of N-methanesulfonyl-1,2-dihydropyridine (1.43 g, 9.0 mmol) in 50 ml dry ether was added to a solution of cyanogen azide prepared from cyanogen bromide (2.65 g, 0.025 mol) and sodium azide (8.12 g, 0.125 mol) in 100 ml dry acetonitrile under a nitrogen atmosphere at 25°. The reaction was allowed to proceed for 20 hr at 25° and completed as described under Procedure E to give a red oil. Preparative tlc was effected on ten 8 x 8 inch silica gel G plates, 0.75 mm in thickness, using benzene - ethyl acetate (2:1 v/v) as the development solvent. Extraction of the band having R_f 0.91 with 50 ml warm methanol gave unreacted N-methanesulfonyl-1,2-dihydropyridine (0.575 g, 40.1%). Extraction of the fraction having R_f 0.34 afforded a 1:1 mixture of syn-N-methanesulfonyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXVIIa) and anti-N-methanesulfonyl-1,2,3,4-tetrahydro-

pyridylidene-4-cyanamide (LXXXVIIb) (0.259 g, 14.5%); ir (neat): 2180 cm^{-1} (C≡N), 1580 cm^{-1} (C=N) and 1550 cm^{-1} (C=C); nmr: δ 2.91 (LXXXVIIb) and 3.05 (LXXXVIIa) (m, 2, C_3-H), 3.14 (s, 3, SO_2CH_3), 3.93 (t($J_{2,3}$ = 7.5 Hz), 2, C_2-H), 5.67 (LXXXVIIa) and 5.96 (LXXXVIIb) (d($J_{5,6}$ = 8 Hz), 1, C_5-H), 7.57 (d($J_{5,6}$ = 8 Hz), 1, C_6-H); mass calcd. for $C_7H_9N_3O_2{}^{32}S$, 199.0415; found, 199.0414.

Syn-N-methoxycarbonyl-2-phenyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXVIIIa) and anti-N-methoxycarbonyl-2-phenyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXVIIIb)

4.4.2.7.1 From N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine and cyanogen azide

A solution of N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (1.53 g, 7.2 mmol) in 25 ml dry ether was added to a solution of cyanogen azide prepared from cyanogen bromide (0.795 g, 7.5 mmol) and sodium azide (2.44 g, 37.5 mmol) in 50 ml acetonitrile under a nitrogen atmosphere at 25°. The reaction was allowed to proceed at 25° for 72 hr and completed as described under Procedure E to give a reddish-black semi-solid. Preparative tlc was effected on eight 8 x 8 inch silica gel G plates, 0.75 mm in thickness, using benzene - ethyl acetate (9:1 v/v) as the development solvent. Extraction of the fraction having R_f 0.78 with 50 ml warm methanol gave N-methoxycarbonyl-2-phenyl-1,2-dihydropyridine (1.03 g, 66.3%). Extraction of the band having R_f 0.27 afforded a 1:1 mixture of syn-N-methoxycarbonyl-2-phenyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide

(LXXXVIIIa) and anti-N-methoxycarbonyl-2-phenyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (LXXXVIIIb) (0.27 g, 14.6%); ir: 2180 cm^{-1} (C≡N), 1730 cm^{-1} (C=O), 1590 cm^{-1} (C=N) and 1560 cm^{-1} (C=C); nmr: δ 3.07 (LXXXVIIIb) and 3.53 (LXXXVIIIa) (m, 1, C_3-H'), 3.26 (LXXXVIIIb) and 3.35 (LXXXVIIIa) (m, 1, C_3-H), 3.90 (s, 3, OCH_3), 5.72 (m, 1, C_2-H), 5.73 (LXXXVIIIa) and 6.10 (LXXXVIIIb) (d($J_{5,6}$ = 8 Hz), 1, C_5-H), 7.3 (m, 5, C_6H_5), 7.98 (d($J_{5,6}$ = 8 Hz), 1, C_6-H); mass calcd. for $C_{14}H_{13}N_3O_2$, 255.1008; found, 255.1008.

Syn-N-methoxycarbonyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCa) and anti-N-methoxycarbonyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCb)

4.4.2.8.1 From N-methoxycarbonyl-2-n-butyl-1,2-dihydropyridine (LXXXIX) and cyanogen azide

A solution of N-methoxycarbonyl-2-n-butyl-1,2-dihydropyridine (LXXXIX) (0.663 g, 3.4 mmol) in 25 ml of dry ether was added with stirring to a solution of cyanogen azide prepared from cyanogen bromide (0.53 g, 5.0 mmol) and sodium azide (1.62 g, 25.0 mmol) in 50 ml of dry acetonitrile under a nitrogen atmosphere at 25°. The reaction was allowed to proceed at 25° for 8 hr and completed as described under Procedure E to yield a reddish-black semi-solid. Preparative tlc was effected on nine 8 x 8 inch silica gel G plates, 0.75 mm in thickness using benzene - ethyl acetate (9:1 v/v) as the development solvent. Extraction of the fraction having R_f 0.81 with 50 ml warm methanol gave N-methoxycarbonyl-2-n-butyl-1,2-dihydropyridine (LXXXIX) (0.144g,

21.7%). Extraction of the band with R_f 0.46 afforded a 1:1 mixture of syn-N-methoxycarbonyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCa) and anti-N-methoxycarbonyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCb) (0.332 g, 41.6%); uv (λ max): 338 nm (N-C=C-C=N); ir: 2180 cm^{-1} (C≡N), 1730 cm^{-1} (C=O), 1580 cm^{-1} (C=N) and 1560 cm^{-1} (C=C); nmr δ 0.88 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.8 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 2.72 (XCb) and 3.16 (XCa) (m, 1, C_3-H'), 2.83 (XCb) and 2.93 (XCa) (m, 1, C_3-H), 3.89 (s, 3, OCH_3), 4.5 (m, 1, C_2-H), 5.68 (XCa) and 5.97 (XCb) (d($J_{5,6}$ = 8 Hz) of d($J_{3,5}$ = 1.25 Hz), 1, C_5-H), 7.72 (d($J_{5,6}$ = 8 Hz) of d($J_{2,6}$ = 1.0 Hz), 1, C_6-H); mass calcd. for $C_{12}H_{17}N_3O_2$, 235.1321; found, 235.1317.

N-acetyl-6-n-butyl-2-diazo-1,2,3,6-tetrahydropyridylidene-3-cyanamide (XCII), syn-N-acetyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCIa), anti-N-acetyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCIb) and 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII)

4.4.2.9.1 From N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) and cyanogen azide

A solution of N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) (3.58 g, 0.02 mol) in 50 ml of dry ether was added slowly with stirring at 25° under a nitrogen atmosphere to a solution of cyanogen azide prepared from cyanogen bromide (2.65 g, 0.025 mol) and sodium azide (8.12 g, 0.125 mol) in 100 ml dry acetonitrile. The reaction was allowed to proceed for 1 hr and completed as described under Procedure E to give a red semi-solid. Preparative tlc was effected on six 8 x 8 inch

silica gel G plates, 0.75 mm in thickness , using benzene - ether (1:2 v/v) as development solvent. Extraction of the band having R_f 0.86 with 50 ml warm methanol gave unreacted N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) (1.6 g, 44.7%). Extraction of the band having R_f 0.58 yielded N-acetyl-6-n-butyl-2-diazo-1,2,3,6-tetrahydropyridylidene-3-cyanamide (XCII) (0.192 g, 3.9%); ir: 2180 cm^{-1} (C≡N), 2090 cm^{-1} (N_2=C), 1700 cm^{-1} (C=O), 1555 cm^{-1} (C=N) and 1545 cm^{-1} (C=C); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.9 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 2.5 (s, 3, $COCH_3$), 5.11 (m, 1, C_6-H), 5.70 - 6.25 (m, 2, C_4-H); mass calcd. for $C_{12}H_{15}N_5O$, 245.1276; found, 245.1271. Similar extraction of the fraction having R_f 0.47 afforded a 3:1 mixture of 3-n-butyl-7-cyano-2,7-diazabicyclo [4.1.0] hept-4-ene (LXXIII) and the isomeric <u>syn</u>-N-acetyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCIa) and <u>anti</u>-N-acetyl-2-n-butyl-1,2,3,4-tetrahydropyridylidene-4-cyanamide (XCIb). The yields were calculated using the nmr integrals for C_3-H of LXXIII and C_2-H of XCIa and XCIb and were found to be LXXIII (0.894 g, 25.3%) and XCIa and XCIb (0.298 g, 7.2%) respectively. This mixture contained all signals present in the ir and nmr spectra of LXXIII prepared from 2-n-butyl-1,2-dihydropyridine (LVI) and cyanogen azide as described previously. The mixture also contained those absorptions present in the ir and nmr spectra of XCIa and XCIb described below. Reaction of N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) (3.58 g, 0.02 mol) and cyanogen azide prepared from equimolar quantities of cyanogen bromide (2.65 g, 0.025 mol) and sodium azide (1.625 g, 0.025 mol) as described

under Procedure C gave a 1:1 mixture of XCIa and XCIb; mp: 71°; ir: 2180 cm^{-1} (C≡N), 1700 cm^{-1} (C=O), 1580 cm^{-1} (C=N) and 1560 cm^{-1} (C=C); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.8 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$) 2.4 (s, 3, $COCH_3$), 2.58 (XCIb) and 3.16 (XCIa) (d($J_{3,3'}$ = 16 Hz), 1, C_3-H'), 2.70 (XCIb) and 2.81 (XCIa) (d($J_{3,3'}$ = 16 Hz) of d ($J_{2,3}$ = 7.5 Hz), 1, C_3-H), 4.76 (m, 1, C_2-H), 5.49 (XCIa) and 5.78 (XCIb) (d($J_{5,6}$ = 8 Hz), 1, C_5-H), 7.33 (d($J_{5,6}$ = 8 Hz), 1, C_6-H); mass calcd. for $C_{12}H_{17}N_3O$, 219.1372; found 219.1372.

Reaction of N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) (1.79 g, 0.01 mol) with cyanogen azide prepared from cyanogen bromide (5.3 g, 0.05 mol) and sodium azide (9.75 g, 0.15 mol) as described above afforded LVII (0.0705 g, 3.9%), XCII (0.47 g, 19.4%), LXXIII (0.348 g, 19.7%) and XCIa and XCIb (0.755 g, 36.5%).

<u>6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridylidene-2-methanesulfonamide (XCVII) and 3-n-butyl-7-methanesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (XCVIII)</u>

4.4.3.1.1 From 2-n-butyl-1,2-dihydropyridine (LVI) and methanesulfonyl azide

<u>General Procedure F</u>

A solution of 2-n-butyl-1,2-dihydropyridine (LVI) (2.74 g, 0.02 mol) containing lithium hydroxide (0.024 g, 0.001 mol) in 50 ml anhydrous ether prepared as described under Procedure A was added slowly with stirring to a solution of methanesulfonyl azide (2.42 g, 0.02 mol) in 50 ml dry ether under a nitrogen atmosphere at 0°. The reaction

was allowed to proceed 1 hr at 0^{o} before warming to 25^{o}. Addition of water (50 ml), extraction with chloroform (2x50 ml), drying (sodium sulfate) and removal of the solvent in vacuo afforded a reddish-black semi-solid which was subjected to preparative tlc on six 8 x 8 inch silica gel G plates, 0.75 mm in thickness, using benzene - ethyl acetate (2:1 v/v) as development solvent. Extraction with warm methanol (50 ml) of the band having R_f 0.59 gave 6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridylidene-2-methanesulfonamide (XCVII) (0.894 g, 17.5%); ir: 3290 cm^{-1} (NH), 2090 cm^{-1} (N_2), 1580 cm^{-1} (C=N); nmr: δ 0.96 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.15 - 1.85 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 3.02 (s, 3, SO_2CH_3), 4.33 (m, 1, C_6-H), 5.3 (d($J_{4,5}$ = 10 Hz) of d ($J_{5,6}$ = 4 Hz) of d($J_{1,5}$ = 1.5 Hz), 1, C_5-H), 6.11 (d($J_{4,5}$ = 10 Hz) of d($J_{4,6}$ = 1.5 Hz), 1, C_4-H), 8.1 (broad s, 1, NH, exchanges with deuterium oxide); mass calcd. for $C_{10}H_{16}N_4O_2{}^{32}S$, 256.0994; found, 256.0984. Extraction of the band with R_f 0.51 afforded 2-n-butylpyridine (0.21 g, 7.7%). Extraction of the band with R_f 0.36 yielded 3-n-butyl-7-methanesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (XCVIII) (1.974 g, 42.9%); ir: 3280 cm^{-1} (NH), 1600 cm^{-1} (C=C); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.8 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 2.93 (s, 3, SO_2CH_3), 3.06 (m, 2, C_1-H, C_6-H), 4.05 (m, 1, C_3-H), 5.76 (m, 2, C_4-H, C_5-H), 8.40 (broad s, 1, NH exchanges with deuterium oxide); mass calcd. for $C_{10}H_{18}N_2O_2{}^{32}S$, 230.1089; found, 230.1085.

Reaction of 2-n-butyl-1,2-dihydropyridine (LVI) (2.70 g, 0.02 mol) prepared as described under Procedure D in 67 ml of dry ether with methanesulfonyl azide (2.42 g, 0.02 mol) as described above afforded

3-n-butyl-7-methanesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (XCVIII) (4.60g, 100%).

6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-methanesulfonamide (C)

4.4.3.1.2 From 3-n-butyl-7-methanesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (XCVIII)

Elution of 3-n-butyl-7-methanesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (XCVIII) (0.364 g, 1.6 mmol) from a neutral alumina column (Brockman Activity I) 2.5 x 20 cm using benzene - ethyl acetate (4:1 v/v) (400 ml) gave 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-methanesulfonamide (C) in quantitative yield; ir (neat): 3310 cm^{-1} (NH), 1640 cm^{-1} (C=C), 1580 cm^{-1} (C=N); nmr: δ 0.91 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.8 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 2.42 (m, 2, C_5-H), 2.97 (s, 3, SO_2CH_3), 3.6 (m, 1, C_6-H), 5.92 (m, 1, C_3-H), 6.7 (d ($J_{3,4}$ = 10 Hz) of d($J_{4,5}$ = 5 Hz) of d ($J_{4,5'}$ = 3.5 Hz), 1, C_4-H); mass calcd. for $C_{10}H_{18}N_2O_2{}^{32}S$, 230.1089; found 230.1085.

6-n-butylpiperidylidene-2-methanesulfonamide (CI) and 6-n-butyl-pyridyl-2-methanesulfonamide (CII)

4.4.3.1.3 From 3-n-butyl-7-methanesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (XCVIII) or 6-n-butyl-1,2,5,6-tetrahydro-pyridylidene-2-methanesulfonamide (C)

Hydrogenation of 3-n-butyl-7-methanesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (XCVIII) (0.121 g, 0.526 mmol) or 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-methanesulfonamide (C) (0.181 g, 0.787 mmol) in 75 ml methanol using 75 mg 10% palladium on charcoal and hydrogen

gas at 35 psi for 4 hr at 25° followed by filtration and removal of the solvent in vacuo gave a colorless oil. Preparative tlc was effected on two 8 x 8 inch silica gel G plates, 0.75 mm in thickness, using benzene - ethyl acetate (1:2 v/v) as the development solvent. Extraction of the band having R_f 0.91 with 50 ml methanol afforded 6-n-butylpyridyl-2-methanesulfonamide (CII) (0.009 g, 7.5% and 0.014 g, 7.8% respectively); ir: 3240 cm^{-1} (NH); nmr: δ 0.93 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.9 (m, 4, $CH_2\underline{CH_2CH_2}CH_3$), 2.7 (t(J = 7 Hz), 2, $\underline{CH_2}CH_2CH_2CH_3$), 3.17 (s, 3, SO_2CH_3), 6.67 (d($J_{3,4}$ = 7.5 Hz) of d ($J_{3,5}$ = 1.0 Hz), 1, C_3-H), 6.98 (d($J_{4,5}$ = 9.0 Hz) of d($J_{3,5}$ = 1.0 Hz), 1, C_5-H), 7.6 (d($J_{4,5}$ = 9.0 Hz) of d($J_{3,4}$ = 7.5 Hz), 1, C_4-H), 8.4 (broad s, 1, NH, exchanges with deuterium oxide); mass calcd. for $C_{10}H_{16}N_2O_2{}^{32}S$, 228.0932; found, 228.0930. Extraction of the band having R_f 0.46 afforded 6-n-butylpiperidylidene-2-methanesulfonamide (CI) (0.112 g, 91.8% and 0.167 g, 91.5% respectively); ir: 3280 cm^{-1} (NH), 1600 cm^{-1} (C=N); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 2.15 (m, 10, $\underline{CH_2CH_2CH_2}CH_3$, C_4-H, C_5-H), 2.46 (m, 2, C_3-H), 2.95 (s, 3, SO_2CH_3), 3.37 (m, 1, C_6-H), 8.3 (broad s, 1, NH, exchanges with deuterium oxide); mass calcd. for $C_{10}H_{20}N_2O_2{}^{32}S$, 232.1245; found, 232.1244.

<u>6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridylidene-2-benzenesulfonamide (CIII) and 3-n-butyl-7-benzenesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CIV)</u>

4.4.3.2.1 From 2-n-butyl-1,2-dihydropyridine (LVI) and benzenesulfonyl azide

A solution of 2-n-butyl-1,2-dihydropyridine (LVI) (2.74 g, 0.02 mol) containing lithium hydroxide (0.024 g, 0.001 mol) in 50 ml of dry ether prepared as described under Procedure A was added slowly with stirring to a solution of benzenesulfonyl azide (3.67 g, 0.02 mol) in 50 ml dry ether under a nitrogen atmosphere at 0^{o}. The reaction was completed as described under Procedure F to afford a reddish-black semi-solid which was subjected to preparative tlc using six 8 x 8 inch silica gel G plates, 0.75 mm in thickness, with benzene - ethyl acetate (4:1 v/v) as development solvent. Extraction of the band having R_f 0.68 using warm methanol (50 ml) gave 6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridylidene-2-benzenesulfonamide (CIII) (2.17 g, 34.1%); mp: 103-104^{o} (decomp. with evolution of gas); ir: 3280 cm^{-1} (NH), 2090 cm^{-1} (N_2) and 1570 cm^{-1} (C=N); nmr: δ 0.85 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.05 - 1.8 (m, 6, $\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_3$), 4.3 (m, 1, C_6-H), 5.2 (d($J_{4,5}$ = 10.5 Hz) of d($J_{5,6}$ = 4 Hz) of d ($J_{1,5}$ = 1.5 Hz), 1, C_5-H), 6.04 (d($J_{4,5}$ = 10.5 Hz) of d($J_{4,6}$ = 1.25 Hz), 1 C_4-H), 7.5 (m, 3, meta and para phenyl hyrogens), 7.98 (m, 2, ortho phenyl hydrogens), 8.26 (broad s, 1, NH, exchanges with deuterium oxide); mass calcd. for $C_{15}H_{18}N_4O_2{}^{32}S$, 318.1150; found, 318.1137. Extraction of the band with R_f 0.53 afforded 3-n-butyl-7-benzene-sulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CIV) (2.38 g, 40.7%); mp: 106^{o}; ir: 3205 cm^{-1} (NH), 1600 cm^{-1} (C=C); nmr: δ 0.88 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.8 (m, 6, $\underline{CH_2}\underline{CH_2}\underline{CH_2}CH_3$), 3.06 (m, 2, C_1-H, C_6-H), 4.07 (m, 1, C_3-H), 5.72 (m, 2, C_4-H, C_5-H), 7.5 (m, 3, meta and para phenyl hydrogens), 7.98 (m, 2, ortho phenyl

hydrogens), 8.78 (broad s, 1, NH, exchanges with deuterium oxide); mass calcd. for $C_{15}H_{20}N_2O_2{}^{32}S$, 292.1245; found, 292.1232.

Reaction of 2-n-butyl-1,2-dihydropyridine (LVI) (2.70 g, 0.02 mol) prepared as described under Procedure D in 67 ml dry ether with benzenesulfonyl azide (3.67 g, 0.02 mol) as described above yielded 3-n-butyl-7-benzenesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CIV) (5.84 g, 100%).

<u>6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridylidene-2-(N-acetyl)sulfanilamide (CV) and 3-n-butyl-7-(N-acetyl)sulfanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CVI)</u>

4.4.3.3.1 From 2-n-butyl-1,2-dihydropyridine (LVI) and N-acetylsulfanilyl azide

A solution of 2-n-butyl-1,2-dihydropyridine (LVI) (1.37 g, 0.01 mol) containing lithium hydroxide (0.024 g, 0.001 mol) in 50 ml dry ether, prepared as described under Procedure A, was added slowly with stirring to a solution of N-acetylsulfanilyl azide (2.42 g, 0.01 mol) in 75 ml ether - acetonitrile (2:1 v/v) under a nitrogen atmosphere at 0^{o}. The reaction was completed as described under Procedure F to afford a red semi-solid which was subjected to preparative tlc on six 8 x 8 inch silica gel G plates, 0.75 mm in thickness using benzene - ethyl acetate (1:2 v/v) as development solvent. Extraction of the band having R_f 0.45 with warm methanol (50 ml) gave 6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridylidene-2-(N-acetyl)sulfanilamide (CV) (0.471 g, 12.5%); mp: 77^{o} (decomp. with evolution of a gas); ir: 3300 cm^{-1} (NH), 3180 cm^{-1} (CONH), 2090 cm^{-1} ($=N_2$), 1585 cm^{-1} (C=N);

nmr: δ 0.8 (m, 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.05 - 1.8 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 2.17 (s, 3, $COCH_3$), 4.26 (m, 1, C_6-H), 5.2 (d($J_{4,5}$ = 10 Hz) of d ($J_{5,6}$ = 4 Hz) of d($J_{1,5}$ = 1.25 Hz), 1, C_5-H), 5.98 (d($J_{4,5}$ = 10 Hz) of d($J_{4,6}$ = 1.25 Hz), 1, C_4-H), 7.73 (m, 4, C_6H_4), 8.1 (broad s, 1, NH, exchanges with deuterium oxide), 8.68 (broad s, 1, CONH, exchanges with deuterium oxide). Extraction of the band at R_f 0.26 yielded 3-n-butyl-7-(N-acetyl)sulfanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CVI) (2.76 g, 79%); mp: 126°; ir: 3300 cm^{-1} (NH), 3180 cm^{-1} (CONH), 1675 cm^{-1} (C=O) and 1590 cm^{-1} (C=C); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.05 - 1.8 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 2.18 (s, 3, $COCH_3$), 3.06 (m, 2, C_1-H, C_6-H), 4.1 (m, 1, C_3-H), 5.75 (m, 2, C_4-H, C_5-H), 7.8 (m, 4, C_6H_4), 8.7 (broad s, 1, NH, exchanges with deuterium oxide), 9.0 (s, 1, CONH, exchanges with deuterium oxide); mass calcd. for $C_{17}H_{23}N_3O_3{}^{32}S$, 349.1460; found, 349.1463.

Reaction of 2-n-butyl-1,2-dihydropyridine (LVI) (0.685 g, 5 mmol) prepared as described under Procedure D in 17 ml dry ether with N-acetylsulfanilyl azide (1.2 g, 5 mmol) in 50 ml ether - acetonitrile (2:1 v/v) as described above afforded 3-n-butyl-7-(N-acetyl)sulfanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CVI) (1.75 g, 100%).

<u>6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridylidene-2-sulfanilamide (CVII) and 3-n-butyl-7-sulfanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CVIII)</u>

4.4.3.4.1 From 2-n-butyl-1,2-dihydropyridine (LVI) and sulfanilyl azide

A solution of 2-n-butyl-1,2-dihydropyridine (LVI) (1.37 g, 0.01 mol) containing lithium hydroxide (0.024 g, 0.001 mol) in 50 ml dry ether, prepared as described under Procedure A, was added slowly with stirring to a solution of sulfanilyl azide (1.98 g, 0.01 mol) in 50 ml ether under a nitrogen atmosphere at 0^{o}. The reaction was allowed to proceed for 1 hr at 0^{0} and then completed as described under Procedure F to afford an orange solid which was subjected to preparative tlc on six 8 x 8 inch silica gel G plates, 0.75 mm in thickness, using benzene - ethyl acetate (1:2 v/v) as development solvent. Extraction of the fraction having R_f 0.88 using 50 ml warm methanol gave 6-n-butyl-3-diazo-1,2,3,6-tetrahydropyridylidene-2-sulfanilamide (CVII) (0.042 g, 1.3%); mp: 134^{o} (decomp. with evolution of a gas); ir: 3460 cm^{-1} (NH_2), 3360 cm^{-1} (NH_2), 3310 cm^{-1} (NH), 2090 cm^{-1} (N_2) and 1590 cm^{-1} (C=N); nmr: δ 0.88 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.05 - 1.8 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 4.27 (m, 3, C_6-H, NH_2, exchanges with deuterium oxide), 5.2 (d($J_{4,5}$ = 10 Hz) of d($J_{5,6}$ = 4 Hz) of d ($J_{1,5}$ = 1.5 Hz), 1, C_5-H), 6.0 (d($J_{4,5}$ = 10 Hz) of d($J_{4,6}$ = 1.25 Hz), 1, C_4-H), 6.68 (m, 2, ortho amino phenyl hydrogens), 7.72 (m, 2, ortho sulfonyl phenyl hydrogens), 8.16 (broad s, 1, NH, exchanges with deuterium oxide). Extraction of the band having R_f 0.54 afforded 3-n-butyl-7-sulanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CVIII) (2.41 g, 78.5%); mp: 132^{o}; ir: 3460 cm^{-1} (NH_2), 3360 cm^{-1} (NH_2), 3290 cm^{-1} (NH) and 1590 cm^{-1} (C=C); nmr (DMSO-d_6): δ 0.87

(t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.8 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 3.0 (m, 2, C_1-H, C_6-H), 4.1 (m, 1, C_3-H), 4.8 (broad s, 2, NH_2 exchanges with deuterium oxide), 5.71 (m, 2, C_4-H, C_5-H), 6.7 (m, 2, ortho amino phenyl hydrogens), 7.65 (m, 2, ortho sulfonyl phenyl hydrogens), 8.6 (broad s, 1, NH, exchanges with deuterium oxide); mass calcd. for $C_{15}H_{21}N_3O_2{}^{32}S$, 307.1355; found 307.1353.

Reaction of 2-n-butyl-1,2-dihydropyridine (LVI) (0.274 g, 2 mmol) prepared as described under Procedure D with sulfanilyl azide (0.396 g, 2.0 mmol) in 50 ml dry ether as described above afforded 3-n-butyl-7-sulfanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CVIII) (0.614 g, 100 %).

6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-sulfanilamide (CIX)

4.4.3.4.2 From 3-n-butyl-7-sulfanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CVIII)

Elution of 3-n-butyl-7-sulfanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CVIII) (1.73 g, 5.6 mmol) from a neutral alumina column (Brockman Activity I) 2.5 x 20 cm after standing for 1 week using chloroform - ethyl acetate (19:1 v/v) gave 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-sulfanilamide (CIX) (1.6 g, 92%); mp: 162°; ir: 3450 cm^{-1} (NH_2), 3350 cm^{-1} (NH_2), 3320 cm^{-1} (NH), 1630 cm^{-1} (C=C) and 1580 cm^{-1} (C=N); nmr: δ 0.95 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.8 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 2.34 (m, 2, C_5-H), 3.55 (m, 1, C_6-H), 4.2 (m, 2, NH_2, exchanges with deuterium oxide), 5.95 (d($J_{3,4}$ = 10 Hz) of d($J_{3,5}$ = 2 Hz), 1, C_3-H), 6.6 (m, 1, C_4-H), 6.65 (m, 2, ortho amino phenyl hydrogens), 7.75 (m, 2, ortho sulfonyl phenyl hydrogens),

8.1 (broad s, 1, NH, exchanges with deuterium oxide); mass calcd. for $C_{15}H_{21}N_3O_2{}^{32}S$, 307.1354; found, 307.1364.

6-n-butylpiperidylidene-2-sulfanilamide (CX)

4.4.3.4.3 From 3-n-butyl-7-sulfanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CVIII) or 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-sulfanilamide (CIX)

Hydrogenation of 3-n-butyl-7-sulfanilyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CVIII) (1.74 g, 5.6 mmol) or 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-sulfanilamide (CIX) (0.116 g, 0.38 mmol) in 100 ml methanol using 0.93 g 10% palladium on charcoal and hydrogen gas at 35 psi for 4 hr at 25° followed by filtration and removal of the solvent in vacuo gave 6-n-butylpiperidylidene-2-sulfanilamide (CX) in quantitative yield; mp: 136°; ir: 3455 cm^{-1} (NH_2), 3355 cm^{-1} (NH_2), 3300 cm^{-1} (NH) and 1590 cm^{-1} (C=N); nmr: δ 0.86 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 2.1 (m, 10, $\underline{CH_2CH_2CH_2}CH_3$, C_4-H, C_5-H), 2.4 (m, 2, C_3-H), 3.3 (m, 1, C_6-H), 4.5 (broad s, 2, NH_2, exchanges with deuterium oxide), 6.6 (m, 2, ortho amino phenyl hydrogens), 7.65 (m, 2, ortho sulfonyl phenyl hydrogens), 8.37 (broad s, NH, exchanges with deuterium oxide); mass calcd. for $C_{15}H_{23}N_3O_2{}^{32}S$, 309. 1511; found, 309.1516.

6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-phenylcarbonylamide (CXI)

4.4.3.5.1 From 2-n-butyl-1,2-dihydropyridine (LVI) and benzoyl azide

A solution of 2-n-butyl-1,2-dihydropyridine (LVI) (2.74 g, 0.02 mol) in 67 ml dry ether prepared as described under Procedure D

was added slowly with stirring to a solution of benzoyl azide (2.94 g, 0.02 mol) in 50 ml dry ether under a nitrogen atmosphere at 25°. The reaction was allowed to proceed for 24 hr and then completed as described under Procedure F to afford a red oil which was subjected to preparative tlc on six 8 x 8 inch silica gel G plates, 0.75 mm in thickness, using benzene - ether (3:1 v/v) as development solvent. Extraction of the band having R_f 0.93 with 50 ml methanol afforded unreacted benzoyl azide (1.4 g, 47.7%). Extraction of the fraction having R_f 0.61 gave rise to 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-phenylcarbonylamide (CXI) (1.03 g, 20.1%); ir: 3180 cm^{-1} (NH), 1640 cm^{-1} (C=O), 1595 cm^{-1} (C=C) and 1560 cm^{-1} (C=N); nmr: δ (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.9 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 2.38 (m, 2, C_5-H), 3.6 (m, 1, C_6-H), 6.14 (d($J_{3,4}$ = 10 Hz) of d($J_{3,5}$ = 2.0 Hz) of d($J_{3,5'}$ = 1.5 Hz), 1, C_3-H), 6.6 (d($J_{3,4}$ = 10 Hz) of d($J_{4,5}$ = 5.0 Hz) of d($J_{4,5'}$ = 3.5 Hz), 1, C_4-H), 7.4 (m, 3, meta and para phenyl hydrogens), 8.3 (m, 2, ortho phenyl hydrogens), 10.6 (broad s, 1, NH, exchanges with deuterium oxide); mass calcd. for $C_{16}H_{20}N_2O$, 256.1576; found, 256.1573. Extraction of the band having R_f 0.36 afforded 2-n-butylpyridine (LVIII) (0.43 g, 15.9%).

Reaction of 2-n-butyl-1,2-dihydropyridine (LVI) (1.37 g, 0.01 mol) with benzoyl azide (7.35 g, 0.05 mol) as described above afforded 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-phenylcarbonylamide (CXI) (1.016 g, 39.7%) and 2-n-butylpyridine (LVIII) (0.208 g, 15.4%).

3-n-butyl-7-methoxycarbonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CXII)

4.4.3.6.1 From 2-n-butyl-1,2-dihydropyridine (LVI) and methoxycarbonyl azide

A solution of 2-n-butyl-1,2-dihydropyridine (LVI) (1.37 g, 0.01 mol) in 33 ml dry ether prepared as described under Procedure D was added slowly with stirring to a solution of methoxycarbonyl azide (1.01 g, 0.01 mol) in 50 ml dry ether under a nitrogen atmosphere at 25°. The reaction was allowed to proceed for 1 hr and then completed as described under Procedure F to afford 3-n-butyl-7-methoxycarbonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CXII) (2.1 g, 100%); ir (neat): 3210 cm^{-1} (NH), 1730 cm^{-1} (C=O) and 1590 cm^{-1} (C=C); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.9 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 3.1 (m, 2, C_1-H, C_6-H), 3.75 (s, 3, OCH_3), 4.1 (m, 1, C_3-H), 5.82 (m, 2, C_4-H, C_5-H), 9.8 (broad s, 1, NH, exchanges with deuterium oxide); mass calcd. for $C_{11}H_{18}N_2O_2$, 210.1368; found, 210.1365.

6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-methoxycarbonylamide (CXIII)

4.4.3.6.2 From 3-n-butyl-7-methoxycarbonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CXII)

Preparative tlc of 3-n-butyl-7-methoxycarbonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CXII) (0.432 g, 2.06 mmol) was effected on six 8 x 8 inch silica gel G plates, 0.75 mm in thickness, using benzene - ethyl acetate (1:9 v/v) as development solvent. Extraction of the fraction having R_f 0.28 using methanol (50 ml) afforded 6-n-butyl-1,2,5,6-tetrahydropyridylidene-2-methoxycarbonylamide (CXIII) (0.432 g,

100%); ir (neat): 3260 cm^{-1} (NH), 1650 cm^{-1} (C=O), 1630 cm^{-1} (C=C) and 1570 cm^{-1} (C=N); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 1.8 (m, 6, $\underline{CH_2CH_2CH_2}CH_3$), 2.4 (m, 2, C_5-H), 3.6 (m, 1, C_6-H), 3.73 (s, 3, OCH_3), 6.0 (d($J_{3,4}$ = 10 Hz) of d($J_{3,5}$ = 2.0 Hz) of d($J_{3,5'}$ = 1.5 Hz), 1, C_3-H), 6.6 (d($J_{3,4}$ = 10 Hz) of d($J_{4,5}$ = 5.0 Hz) of d ($J_{4,5'}$ = 3.5 Hz), 1, C_4-H), 9.6 (broad s, 1, NH, exchanges with deuterium oxide); mass calcd. for $C_{11}H_{18}N_2O_2$, 210.1368; found, 210.1365.

<u>6-n-butylpiperidylidene-2-methoxycarbonylamide (CXIVa) and 6-n-butyl-3,4,5,6-tetrahydropyridyl-2-methoxycarbonylamide (CXIVb)</u>

4.4.3.6.3 From 3-n-butyl-7-methoxycarbonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CXII)

Hydrogenation of 3-n-butyl-7-methoxycarbonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CXII) (0.434 g, 2.07 mmol), in 75 ml methanol using 300 mg 10% palladium on charcoal and hydrogen gas at 35 psi for 4 hr at 25° followed by filtration and removal of the solvent <u>in vacuo</u> afforded a light brown oil. Preparative tlc was effected on six 8 x 8 inch silica gel G plates, 0.75 mm in thickness, using ethyl acetate - isopropanol (9:1 v/v) as development solvent. Extraction of the fraction having R_f 0.51 with 50 ml methanol afforded the tautomeric mixture of 6-n-butylpiperidylidene-2-methoxycarbonylamide (CXIVa) and 6-n-butyl-3,4,5,6-tetrahydropyridyl-2-methoxycarbonylamide (CXIVb) (0.278g, 63.4%); ir (neat): 3210 cm^{-1} (NH) (CXIVa) and 3150 cm^{-1} (NH) (CXIVb), 1635 cm^{-1} (C=O) and 1590 cm^{-1} (C=N); nmr: δ 0.9 (t(J = 7 Hz), 3, $CH_2CH_2CH_2\underline{CH_3}$), 1.1 - 2.2 (m, 10, $\underline{CH_2CH_2CH_2}CH_3$,

C_4-H, C_5-H), 2.48 (m, 2, C_3-H), 3.45 (m, 1, C_6-H), 3.71 (s, 3, OCH_3), 10.2 (broad s, 1, NH, exchanges with deuterium oxide); mass calcd. for $C_{11}H_{20}N_2O_2$, 212.1525; found, 212.1522.

6,6'-di-n-butyl-1,2,3,6-tetrahydro-2,3'-dipyridyl (LXIII)

4.4.3.7.1 From 2-n-butyl-1,2-dihydropyridine (LVI) and hydrazoic acid

A solution of 2-n-butyl-1,2-dihydropyridine (LVI) (2.74 g, 0.02 mol) in 67 ml dry ether prepared as described under Procedure D was added slowly with stirring to a solution of hydrazoic acid (34.4 ml of 5.8M, 0.02 mol) in 50 ml dry benzene under a nitrogen atmosphere at 25°. The reaction was allowed to proceed for 24 hr and was completed as described under Procedure F to yield a reddish-brown oil. Preparative tlc was effected on six 8 x 8 inch silica gel G plates, 0.75 mm in thickness, using benzene - methanol (7:1 v/v) as development solvent. Extraction of the band having R_f 0.75 with 50 ml warm methanol afforded 2-n-butylpyridine (LVIII) (0.329 g, 12.2%). Extraction of the band having R_f 0.62 yielded 6,6'-di-n-butyl-1,2,3,6-tetrahydro-2,3'-dipyridyl (LXIII) (0.873 g, 64.7%) which showed ir and nmr spectra identical to those of the compound prepared from N-lithio-2-n-butyl-1,2-dihydropyridine (XXX) and chloramine in section 4.2.2.3.1.

3-n-butyl-7-benzenesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CIV)

4.4.3.8.1 From N-acetyl-2-n-butyl-1,2-dihdyropyridine (LVII) and benzenesulfonyl azide

A solution of N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII)

(3.58 g, 0.02 mol) in 50 ml ether was added to a solution of benzenesulfonyl azide (3.66 g, 0.02 mol) in 100 ml dry ether under a nitrogen atmosphere at 25°. The reaction was allowed to proceed for 90 hr after which water (100 ml) was added. Extraction with chloroform (2x75 ml), drying (sodium sulfate) and removal of the solvent in vacuo yielded a red oil which was subjected to preparative tlc on nine 8 x 8 inch silica gel G plates, 0.75 mm in thickness using benzene - ether (1:2 v/v) as development solvent. Extraction of the band having R_f 0.96 with 50 ml methanol gave unreacted benzenesulfonyl azide (1.67 g, 46.4%). Extraction of the band having R_f 0.86 afforded unreacted N-acetyl-2-n-butyl-1,2-dihydropyridine (LVII) (2.4 g, 67%). Extraction of the fraction having R_f 0.58 yielded 3-n-butyl-7-benzenesulfonyl-2,7-diazabicyclo [4.1.0] hept-4-ene (CIV) (1.55 g, 26.5%) showing ir and nmr spectra identical to those of the compound prepared from 2-n-butyl-1,2-dihydropyridine (LVI) and benzenesulfonyl azide described in section 4.4.3.2.1.

5.0.0.0.0 BIBLIOGRAPHY

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